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# American Journal of Obstetrics and Gynecology

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## Original Communications

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### EXPERIENCE WITH SURGICAL AND RADIATION THERAPY IN CARCINOMA OF THE CORPUS UTERI\*

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TWO HUNDRED AND EIGHTY-THREE patients with carcinoma of the corpus uteri were admitted to the Gynecological Service at the Memorial Hospital during the fifteen-year period from 1918 to 1932. Eighty-six of these cases had residual or recurrent carcinoma after treatment by surgery or radiation elsewhere and are not included in the following review. One hundred and ninety-seven received their primary treatment at the Memorial Hospital, and it is these cases which constitute the subject material for this paper. All but five patients were followed for five years or more or until death. In the statistics which follow, the five patients lost track of are counted as deaths from carcinoma, as are the cases in which the cause of death is not definitely known.

Of this group of 197 patients 93 were treated by a combination of surgery and radiation, 96 received radiation therapy alone, and 8 were treated by surgery alone. All cases were proved histologically to be carcinoma of the corpus uteri. The cases have been classified both clinically and histologically, and these classifications have been correlated with end results as have the various techniques of treatment which were employed.

The age of the patients in this series ranged from 19 to 79. The average age was 58 and the ten-year period of greatest incidence was from 55 to 64. Table I shows how the cases were distributed.

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\*Read at a meeting of the New York Obstetrical Society, November 8, 1938.

TABLE I. AGE

Youngest	19 Average age	Oldest 58	79
10-year period of greatest incidence			55-64
19-40	3%	55-59	25%
40-44	3%	60-64	20%
45-49	12%	65-69	14%
50-54	16%	70-74	5%
	75-79	2%	

Consideration of *marital status* revealed that 83 per cent were married or widowed, 16 per cent single and that in 1 per cent marital status was not stated in the patient's record. Fifty-four per cent of the patients had one or more pregnancies, 36 per cent had never been pregnant, and in 10 per cent information in regard to this point was lacking. It is of interest to mention in this connection that not over 10 per cent of reported cases of patients with carcinoma of the cervix are nulliparous.

The *incidence of previous pelvic operations* was low (12 per cent). Eighty-eight per cent of the patients had no previous pelvic surgery, suggesting at least that the pelvic organs up to the time of the development of carcinoma had not been grossly abnormal.

TABLE II. INCIDENCE OF PREVIOUS PELVIC OPERATIONS

	PER CENT
Oophorectomy	4
Dilatation and curettage	2
Cauterization of cervix	2
Perineal repair	2
Suspension of uterus	1
Myomectomy	1
No previous pelvic operation	88

The *symptoms* of carcinoma of the corpus uteri begin, as a rule, after the menopause. In this series 78 per cent of the patients stated that the onset of symptoms occurred after menstruation had ceased. The average age at menopause was 50 years. The duration of symptoms varied from less than a month to over three years. Thirty-seven of the patients waited longer than a year before seeking medical attention.

The most important and most frequent symptom of carcinoma of the corpus uteri is *uterine bleeding*. It was present in 98 per cent of the entire group of 197 cases. In 97 per cent the bleeding was postmenopausal or intermenstrual, in 1 per cent menorrhagia only was noted. Uterine bleeding was usually slight and intermittent at first, tending to become more constant and profuse as time went on.

*Pain*, for the most part localized in the pelvis and lower abdomen, was present in 27 per cent of the cases and is a symptom of some prognostic significance. Of the 53 patients complaining of pain, 66 per cent later died of carcinoma, whereas of the 144 patients without pain only 37 per cent died of carcinoma. It is also of interest that 43 per cent of the patients complaining of pain when their history was taken and who later died of carcinoma had no palpable evidence of extension beyond the uterus at initial examination. This suggests that pain in some cases at least indicates extension of carcinoma beyond the uterus before such extension can be verified by clinical examination.

*Discharge*, usually watery and nialodorous, was present in at least 35 per cent of the cases, but it was not a prominent symptom in the patients' minds and consequently its presence or absence was not always recorded. It occasionally occurred before the onset of uterine bleeding, but it was in almost every case the bleeding which caused the patient to seek medical advice.

TABLE III. SYMPTOMS

Uterine bleeding		98%
Postmenopausal or intermenstrual	97%	
Menorrhagia only	1%	
No bleeding	1%	
Not stated	1%	
Pain (pelvis, lower abdomen, back)		27%
Discharge		35%
Tumor		1%

TABLE IV. PAIN AS A PROGNOSTIC FACTOR

Number of patients with pain		53
Died of carcinoma	35 or 66%	
Number of patients without pain		144
Died of carcinoma	53 or 37%	

Information in regard to the *association* of carcinoma of the corpus with *fibromyoma* was gained from a review of the 101 cases which were subjected to abdominal operation. Thirty-eight per cent of these were found to have both fibromyoma and carcinoma of the body of the uterus. This serves to emphasize the fact that the source of uterine bleeding cannot be considered as nonmalignant just because fibroids are palpable. An examination of endometrial tissue is a prerequisite to an accurate diagnosis.

The entire series of 197 cases was divided into clinical groups according to the extent of the carcinoma as evidenced by observation and palpation. Into Group I were placed those patients in whom there was no palpable enlargement of the uterus. Group II was made up of patients in whom the uterus was enlarged but was not over the size of a two and one-half months' gestation. Approximately half of all of the cases fell into this group. This size (two and one-half months' gestation) was not decided on arbitrarily but was arrived at by first determining the survival rates for several different degrees of enlargement. A sharp drop in five-year survivals was found when the uterus was the size of a three, four, or five months' gestation. The point at which the prognosis seemed to become definitely less favorable was when the uterus reached the size of a three months' gestation. Group IIA was reserved for patients in whom the uterus was larger than a two and one-half months' gestation, but in which the disease was still confined to the uterus so far as could be determined clinically. In Group III were placed all cases in which there was evidence of extension beyond the uterus at the time of first examination. Table V indicates the number and percentage of cases in each clinical group.

TABLE V. CARCINOMA OF CORPUS UTERI. CLINICAL GROUPS

CLINICAL GROUP	NUMBER OF CASES	PERCENTAGE
I. Uterus not enlarged	42	22
II. Uterus enlarged but not over size of 2½ mo. gestation	97	49
IIA. Uterus larger than 2½ mo. gestation	20	10
III. Extension of carcinoma beyond uterus	38	19

The next step was to determine the *relation of the clinical groups to prognosis* as evidenced by five-year survivals. It was found that when the uterus was not larger than a two and one-half months' gestation and when there was no clinical evidence of extension of carcinoma beyond the uterus the five-year survival rate was 60 per cent. When the uterus was larger than a two and one-half months' gestation, the five-year survivals were only 35 per cent, and when there was extension of carcinoma beyond the uterus, only 10 per cent of the patients lived five years. These figures are based on clinical group only and are without regard to method of treatment employed. However, it will be seen from consulting Table VII that they roughly parallel those for patients treated by radiation alone and by radiation combined with surgery.

Ninety-six patients were treated by radiation alone and 93 by a combination of radiation and surgery. Only 8 patients were treated by surgery alone, and it is felt that this is too small a group to be of value for comparison of end results with the results of the other methods of treatment. The other two groups, however, are nearly equal and are of sufficient size so that statistics based upon them may be considered as representative of the two types of treatment. It should be stated that decision as to whether treatment should be by radiation followed by complete abdominal hysterectomy or by radiation alone was influenced greatly by the age and general condition of the patient. Those patients treated by radiation alone were for the most part either poor surgical risks due to advanced age, obesity, or intercurrent disease, or were individuals who refused operation. The authors believe that whenever possible intrauterine radiation should be followed by complete abdominal hysterectomy. Statistics to show the reasons for this opinion will be presented presently.

TABLE VI. CARCINOMA OF CORPUS UTERI. RELATION OF CLINICAL GROUP TO PROGNOSIS\*

CLINICAL GROUP	NUMBER OF CASES	5-YEAR SURVIVAL PER CENT	DEATH FROM CARCINOMA IN LESS THAN 1 YEAR PER CENT
I. Uterus not enlarged	42	62	12
II. Uterus enlarged but not over size of 2½ mo. gestation	97	59	5
IIA. Uterus larger than 2½ mo. gestation	20	35	25
III. Extension of carcinoma beyond uterus	38	10	66
Total	197		

\*Without regard to method of treatment employed.

TABLE VII. CARCINOMA OF CORPUS UTERI. RELATION OF CLINICAL GROUP TO END RESULTS UNDER RADIATION ALONE AND RADIATION COMBINED WITH SURGERY

CLINICAL GROUP	RADIATION ALONE		RADIATION AND SURGERY	
	NO. OF CASES	5-YEAR SURVIVAL PER CENT	NO. OF CASES	5-YEAR SURVIVAL PER CENT
I. Uterus not enlarged	24	58	18	67
II. Uterus enlarged but not over size of 2½ mo. gestation	40	55	54	61
IIA. Uterus larger than 2½ mo. gestation	7	0	9	45
III. Extension of carcinoma beyond uterus	25	4	12	17
End result, all cases	96	39	93	55

The outlook when radiation alone must be relied upon is by no means hopeless. In fact results obtained by this method are quite encouraging. The five-year survival rate for all 96 patients treated by radiation alone is 39 per cent. However, when the patients were subdivided into clinical groups, it was found that for the 64 cases falling into Groups I and II, in which the carcinoma appeared to be confined to the uterus on clinical examination and in which the uterus was not larger than a two and one-half months' gestation, the five-year survival rate was 56 per cent.

Of the 7 patients with uteri larger than a two and one-half months' gestation, none survived five years when treated by radiation alone. It is very likely that this increased size of the uterus contributed directly to the poor clinical result by preventing adequate approximation and dosage of radium to all parts of the tumor. Since the intensity of radiation varies inversely as the square of the distance from

the source of radiation, it can readily be seen that a large uterus does not receive the same amount of radiation throughout its body from two radon capsules of given strength lying within the uterine cavity as does a small uterus. For example, it has been calculated that 3,600 millicurie hours from two radon capsules in a uterine cavity delivers approximately seven threshold erythema doses at 1.5 cm. distance, but only one threshold erythema dose at 5 cm., and one-half of a threshold erythema dose at 10 cm. from the radon capsules. Thus it is obvious that a dose which is adequate for a small uterus is totally inadequate for a large one. If the total dose is raised to compensate for this deficiency, necrosis is likely to occur in the uterine wall adjacent to the radon. With external radiation alone by means of 200 kv. x-ray we are not at present able to deliver a sufficient depth dose to cure corpus carcinoma. One must realize therefore that with present technique at least, radiation therapy may not be adequate to control bulky corpus carcinoma and should be supplemented whenever possible by complete hysterectomy. Repeated treatments of not over 1,500 millicurie hours each with three or four capsules may be the best procedure in large uteri when one is compelled to rely on radiation alone. In such cases it is understood that x-ray should also be used if possible. In a similar group of clinical Group IIA cases treated by radiation followed by complete abdominal hysterectomy the five-year survival rate was 45 per cent.

When there is clinical extension of carcinoma beyond the uterus the chance for cure is slight regardless of the method of treatment employed. Nevertheless occa-

TABLE VIII. CARCINOMA OF CORPUS UTERI. HISTOLOGIC TYPES

HISTOLOGIC TYPE	NUMBER OF CASES	PERCENTAGE
Adenoma malignum Grades I and II	95	48.0
Adenocarcinoma Grade II	46	24.0
Adenocarcinoma Grades III and IV	40	20.0
Embryonal adenocarcinoma	2	1.0
Adenoacanthoma	10	5.0
Epidermoid carcinoma	1	0.5
Adenoma malignum and epidermoid carcinoma	1	0.5
Adenoma malignum and myosarcoma	1	0.5
Adenocarcinoma and myosarcoma	1	0.5
	197	

TABLE IX. CARCINOMA OF CORPUS UTERI. RELATION OF HISTOLOGIC TYPE TO PROGNOSIS

HISTOLOGIC TYPE	NUMBER OF CASES	5-YEAR SURVIVAL PER CENT
Adenoma malignum Grades I and II	95	60
Adenocarcinoma Grade II	45	42
Adenocarcinoma Grades III and IV	39	20
Adenoacanthoma	10	60

TABLE X. CARCINOMA OF CORPUS UTERI. RELATION OF HISTOLOGIC TYPE TO END RESULTS UNDER RADIATION ALONE AND RADIATION COMBINED WITH SURGERY

HISTOLOGIC TYPE	RADIATION ALONE		RADIATION AND SURGERY	
	NO. OF CASES	5-YEAR SURVIVAL PER CENT	NO. OF CASES	5-YEAR SURVIVAL PER CENT
Adenoma malignum, Grades I and II	46	39	45	78
Adenocarcinoma, Grade II	29	41	16	44
Adenocarcinoma, Grades III and IV	18	28	21	14
Embryonal adenocarcinoma				
Adenoacanthoma	3	66	7	57
End result, all cases	96	39	89	55

sionally something can be done as evidenced by the fact that 10 per cent of the 38 patients in the entire series which fell into this group lived five years or more. Sixty-six per cent of the patients in this advanced group died in less than one year after initial examination, whereas in the other clinical groups even though the eventual outcome was fatal only 9 per cent died in less than a year.

The five-year survival rate for all of the patients treated by a combination of radiation and surgery regardless of the particular technique employed was 55 per cent. For the cases in clinical Groups I and II it was 63 per cent. For a group of patients treated by what is now considered the most satisfactory technique, the five-year survival rate for all cases including all clinical groups was 79 per cent.

In addition to a classification according to clinical extent of disease the 197 cases on which this study is based were classified according to histologic type. Adenoma malignum Grades I and II made up nearly one-half of the total group. Adenocarcinoma Grade II was next in frequency of occurrence, being present in 24 per cent of the cases. Adenocarcinoma Grades III and IV made up 20 per cent and adenoacanthoma (a glandular tumor which has undergone squamous metaplasia), 5 per cent.

TABLE XI. EFFECT OF RADIATION ON CARCINOMA OF CORPUS

INTRACAVITARY RADON DOSAGE IN MILLICURIE HOURS	NO. OF CASES	COMPLETE REGRESSION	RESIDUAL CARCINOMA
1200-2700	24	3	21
3000-3300	25	13	12
3400-4000	20	12	8
----- Roentgen ray only	6	0	6

An analysis of the relation of histologic type to end results and to type of treatment yielded information of considerable interest. For the entire group regardless of the method of treatment employed, the five-year survival rate for adenoma malignum Grades I and II was 60 per cent, for adenocarcinoma Grade II it was 42 per cent, for adenocarcinoma Grades III and IV it was 20 per cent, and for adenoacanthoma 60 per cent. When the results of the two methods of treatment were compared, it was found that adenoma malignum treated by radiation alone yielded 39 per cent five-year survivals; whereas 78 per cent of the patients with the same lesion treated by radiation followed by hysterectomy were alive five years or more. For adenocarcinoma Grade II, however, the difference is far less, the percentages being 41 and 44, respectively. For adenocarcinoma Grades III and IV and embryonal carcinoma the survival rate was better when radiation alone was used, 28 per cent surviving five years under this treatment and only 14 per cent when radiation was followed by surgery. Adenoacanthoma in a small series of 10 cases had a five-year survival rate of 60 per cent with no significant difference between the two methods of treatment. It should be pointed out that these figures represent results of varied techniques of treatment over a period of fifteen years. For results of the present method of treatment consult Table XII.

In 75 patients subjected to hysterectomy after intrauterine radiation, a careful microscopic examination was performed to determine the presence or absence of residual carcinoma. The effects of different doses of intrauterine radiation were determined. It was found that of six patients who received roentgen ray only, all showed residual carcinoma. In 24 cases in which the intracavitary radon dosage varied from 1,200 to 2,700 millicurie hours complete regression occurred in only 12 per cent. In 25 cases in which the dose was from 3,000 to 3,300 millicurie hours there was complete disappearance of carcinoma in 52 per cent, while in 20 patients receiving 3,400 to 4,000 millicurie hours 60 per cent showed no residual carcinoma. These results in addition to demonstrating the effect of different dosages of intrauterine radon also reveal the fact that in 40 per cent of patients receiving the largest doses (3,400 to 4,000 mc. hr.), there was evidence of residual carcinoma at the time

of hysterectomy. This is an important reason for the authors' view that whenever possible the uterus should be removed. Another important reason of course is the fact that the five-year results for radiation followed by hysterectomy are better than they are for radiation alone. The reason for the use of intrauterine radium six to eight weeks before complete abdominal hysterectomy is twofold. First, it is conceivable that radiated carcinoma even if not completely destroyed is somewhat less likely to enter blood or lymph channels or to remain as viable implants in the pelvis at the time of hysterectomy than is carcinoma which has not been subjected to radiation. Second and far more significant is the fact that the results of the combined method of treatment as now employed are definitely better than those obtained by surgery alone. This is especially true of the patients who receive 3,000 to 4,000 millicurie hours of intrauterine radiation. Of the 28 patients in our series who received this dose and who have been followed five years or more, 79 per cent survived at least five years. Arneson, following a similar plan of treatment had even

TABLE XII. CARCINOMA OF CORPUS UTERI

Intrauterine Radon 3,000-4,000 Millicurie Hours Followed in One to Four Months by Panhysterectomy

CLINICAL GROUP	NO. OF CASES	5-YEAR SURVIVAL PER CENT	FREE OF DISEASE 5 YR. OR MORE PER CENT	DEATH DUE TO CARCINOMA			DEATH FROM OTHER CAUSE IN LESS THAN 5 YEARS	LOST
				LESS THAN 1 YR. PER CENT	1-2 YR. PER CENT	2-4 YR. PER CENT		
I. Uterus not enlarged	5	100	100	0	0	0	0	0
II. Uterus enlarged but not over size of 2½ mo. gestation	20	85	80	10	0	5	0	0
IIA. Uterus larger than 2½ mo. gestation	2	0	0	50	0	50	0	0
III. Extension of carci- noma beyond uterus	1	0	0	100	0	0	0	0
End result, all cases	28	79	75	14	0	7	0	0

TABLE XIII. CARCINOMA OF CORPUS UTERI

Intrauterine Radon 3,000-4,000 Millicurie Hours Followed in One to Four Months by Panhysterectomy

HISTOLOGIC TYPE	NO. OF CASES	5-YEAR SURVIVAL PER CENT	FREE OF DISEASE 5 YR. OR MORE PER CENT	DEATH DUE TO CARCINOMA			DEATH FROM OTHER CAUSE IN LESS THAN 5 YEARS	LOST
				LESS THAN 1 YR. PER CENT	1-2 YR. PER CENT	2-4 YR. PER CENT		
Adenoma malignum Grades I and II	15	100	100	0	0	0	0	0
Adenocarcinoma Grade II	6	50	33	17	0	33	0	0
Adenocarcinoma Grade III	5	40	40	60	0	0	0	0
Adenoacanthoma	2	100	100	0	0	0	0	0
End result, all cases	28	79	75	14	0	7	0	0



better results in a somewhat smaller series. Ward and Sackett at the Women's Hospital in New York have found the combination of radiation and surgery more efficacious than surgery alone, as has Norris in Philadelphia. Arneson recently reviewed the literature on the surgical treatment of corpus cancer and found that of 927 reported cases 57 per cent of the patients were living five years or more.

In the group of 28 patients treated by the method which the authors now consider most desirable all of the cases of adenoma malignum and adenoacanthoma have survived free of clinical evidence of disease for five years or more. The five-year survival rate for adenocarcinoma Grade II is 50 per cent, and for adenocarcinoma Grade III 40 per cent. The five-year survival rate for the entire group of 28 cases, as stated before, is 79 per cent. Of the 28 cases 75 per cent are free of clinical evidence of carcinoma. Tables XII and XIII show the end results of recommended technique of treatment.

The patient's history will often suggest the presence of corpus carcinoma, and if so-radon is held available in the operating room at the time, a diagnostic curettage is done. If the gross appearance of the curettings is suggestive of carcinoma, a radon tandem of two or three capsules, depending on the size of the uterus, is placed within the uterine cavity immediately after the curettage. The radon capsules are each 15 mm. in length, have a combined strength of 75 to 150 millicuries, are filtered by  $\frac{1}{2}$  mm. of platinum and are encased in a small rubber tube the wall of which is 2 mm. thick. A frozen section is done to establish the diagnosis microscopically, and, if carcinoma is found, the radon is allowed to remain in place for a dose of 3,600 millicurie hours. The diagnostic curettage and insertion of radium are done under general anesthesia. The radon tandem is sutured in place by means of a cat-gut suture passed through the cervix and tied in a bow knot so that removal is not difficult. The vagina is packed with sterile gauze and a Pezzer catheter placed in the bladder. The patients are kept in bed until the radium and catheter are removed and for three or four days thereafter. Two weeks after the intrauterine application of radon external radiation by means of 200 kv. roentgen ray is given, 750 r. being given to each of four pelvic ports 11 by 14 cm. in size at a target skin distance of 70 cm., milliamperage of 30, and filtration of  $\frac{1}{2}$  mm. copper. One pelvic portal is treated daily or on alternate days. Six or ten weeks after the completion of radiation a complete abdominal hysterectomy is performed, the entire uterus including the cervix with both tubes and ovaries being removed. One of the first steps in the operation is the closure of the fimbriated ends of the Fallopian tubes by ligature. Care is taken to avoid trauma to the uterus and no tenaculum or forceps is placed on the body of the uterus at any time. A careful and prolonged follow-up is an essential part of the correct treatment of carcinoma of the corpus uteri.

When the diagnosis is quite definite from history and clinical examination, it is considered advisable to give the external radiation two weeks before the curettage and insertion of radium. When radiation alone is to be relied upon, another curettage should be done four to six months after the first curettage or when there is any recurrence of symptoms. If residual carcinoma is found, treatment by intrauterine radon not over 2,500 millicurie hours should be given.

In this series of cases no definite improvement in results from adding roentgen ray to intrauterine radon could be demonstrated. However, it did not appear to cause any complications and should in the authors' opinion be used to supplement radon. Since external radiation of the type described delivers only about one threshold erythema dose throughout the pelvis and since it has been estimated that from 5 to 10 threshold erythemata are necessary for control of corpus carcinoma, it is felt that the intrauterine radon is of chief importance.

Complications following the treatment of carcinoma of the corpus uteri have been few. Of the 96 patients treated by radiation alone, two developed hematuria and one had pyometra. One of the patients complaining of hematuria and dysuria had a radiation ulcer of the bladder which healed after irrigations and the instillation of argyrol. In the other no ulcer was found on cystoscopy and symptoms promptly subsided after bladder irrigations and the instillation of argyrol. The patient who developed pyometra did so one year after treatment which had consisted of the intrauterine application of 3,000 millicurie hours of radon by means of a radon tandem.

There were no complications in the group of 28 cases treated by a combination of radiation and surgery according to the plan outlined above. Among the others in the group of 93 treated by some combination of radiation and surgery there were two vesicovaginal fistulas and one rectovaginal fistula.

One of these patients had adenoma malignum with extension to the cervix when first seen. Radium was applied to both cervix and uterine cavity, the total dose being 5,400 millicurie hours. The patient also received 1,000 millicurie hours postoperatively because of some infiltration in the vaginal vault. In addition she received a pelvic cycle of x-ray both before and after operation. A vesicovaginal fistula developed four months after operation. Two years later a repair was advised but refused. The patient died six years after treatment from an unrelated cause and free of carcinoma. It is felt that overdosage of radiation was probably responsible for the development of a vesicovaginal fistula in this case.

The second patient, also a case of adenoma malignum, received first a tandem for 1,200 millicurie hours, three months later 2,500 millicurie hours, and two years later, because of recurrence, 3,600 millicurie hours. A complete hysterectomy was done two months after this last application of radium and a vesicovaginal fistula developed one year postoperatively. The fistula was closed two and one-half years after operation and there has been no recurrence. In this case also the total dose was probably excessive, although the initial dose was inadequate.

The patient who developed a rectovaginal fistula was histologically adenocarcinoma Grade III. A tandem was inserted for 3,000 millicurie hours and was followed by a pelvic cycle of x-ray. Three years later because of a recurrence of symptoms a tandem was placed in the uterus for 3,300 millicurie hours and another pelvic cycle given. A complete abdominal hysterectomy was done two months later. Three months after operation the patient developed a rectovaginal fistula. The patient is now a nine-year cure but still has her fistula. Inadequate first dose and excessive radiation after recurrence are perhaps etiologic features.

The operative mortality for the 93 patients subjected to hysterectomy following radiation therapy was 4.3 per cent.

The principal cause of death in the entire group of 197 cases was residual or recurrent carcinoma in the pelvis about the vaginal vault, causing hemorrhage or obstruction of the ureters with resultant uremia. Four cases had pulmonary metastases proved by x-ray, one of these cases had metastasis to a cervical node proved by biopsy. Two patients died of carcinoma primary in another part of the body and apparently unrelated to the corpus cancer. One of these developed carcinoma of the breast twelve years after hysterectomy and died of carcinoma of the breast two years later. The other died of squamous carcinoma of the vulva six years after radiation and hysterectomy for adenocarcinoma of the corpus uteri.

#### SUMMARY AND CONCLUSIONS

1. Carcinoma of the corpus uteri is in most instances a postmenopausal disease, uterine bleeding its most constant symptom.

2. Postmenopausal bleeding should at once suggest the presence of carcinoma of the corpus even though the patient has a readily palpable fibromyomatous uterus. These two conditions were found to be associated in 38 per cent of the cases in this series.

3. Pain would appear to be an important prognostic factor. Sixty-six per cent of the patients complaining of pain at the time of first examination later died of carcinoma. In nearly half of these, initial examination revealed no evidence of extension of carcinoma beyond the uterus.

4. The 197 cases of carcinoma of the corpus uteri on which this study has been based fall readily into three principal histologic groups.

Approximately one-half of all cases were adenoma malignum, one-fourth were adenocarcinoma Grade II, and approximately one-fourth adenocarcinoma Grade III or IV. The histologic type bears a direct relation to chance for cure and is of definite prognostic importance. The five-year survival rate for adenoma malignum is appreciably higher than for adenocarcinoma Grade II and, that for adenocarcinoma Grade II is higher than for adenocarcinoma Grades III and IV. The results in a small series of cases of adenoacanthoma indicate that the prognosis in this group is very nearly equal to that for adenoma malignum.

5. It appears worthwhile from both a prognostic and a therapeutic standpoint to subdivide the cases into clinical groups according to size of uterus and palpable extent of disease. If the uterus is not larger than the size of a 2½ months' gestation and if there is no evidence of extension of carcinoma beyond the uterus, the five-year survival rate is 60 per cent if based upon the entire series of 197 cases without regard to method of treatment, and 88 per cent if based on results in a smaller series of cases treated according to what is regarded by us as the preferred method of treatment. If the uterus is larger than a 2½ months' gestation our findings indicate that the chance for cure from radiation alone is extremely low. If there is palpable extension of carcinoma beyond the uterus the chance for five-year survival is approximately 10 per cent.

6. Radiation alone has definite curative value in cases which for one reason or another cannot be subjected to subsequent panhysterectomy, the five-year survival rate for the group of 96 patients treated by radiation alone being 39 per cent. When only clinical Groups I and II are considered the five-year survival is 56 per cent and the five-year cure (free from all evidence of carcinoma five years or more) is 47 per cent.

7. Intrauterine radon, usually not less than 3,600 millicurie hours, supplemented by roentgen ray and followed by panhysterectomy seems to offer the greatest opportunity for cure. Seventy-nine per cent of the patients so treated have survived five years or more and 75 per cent have been free from all evidence of carcinoma for over five years. The risk of any major complication under this plan of treatment seems to be slight.

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121 EAST SIXTIETH STREET

#### DISCUSSION

DR. JAMES A. CORSCADEN.—The best method for treating cancer of the corpus has not been established. Stoeckel of Berlin reports about the same percentage of five-year cures by vaginal hysterectomy and Wintz reports similar figures from x-ray alone.

From our own experience with 144 cases several points may be noted. 25 per cent of the women were unmarried; 43 per cent were nulliparous as compared with 14 per cent for our cancers of the cervix. The average weight of the patients in the corpus cases was 165 pounds and of the cervix cases 128 pounds. Age should influence us little in diagnosis inasmuch as in Dr. Healy's series 15 per cent and in ours 20 per cent were below the age of fifty.

Our clinic is trying to figure out some endocrine predisposition. However, there is a large number of these women who have small hands and feet and large hips. This in connection with the childlessness and low marriage rate is of interest.

We have twenty-one uteri obtained by hysterectomy after previous radiation and in eight of those there was no cancer found. On the other hand, in some cases in which the uterus seemed to be free of cancer, there was a small metatasis in the ovary. These two simple findings lend weight to the mode of therapy advocated. The preliminary radiation gets rid, at least, of the local implantation metastases. The hysterectomy eliminates metastases in the ovaries and those adjacent to the uterus when the glands are not yet involved.

In regard to results: we have only 10 cases which have been treated more than five years both by preliminary radiation and hysterectomy. One of them died in the hospital (an operative death), one other patient died of carcinomatous metastases, and the other eight lived.

Our procedure in the management of uterine bleeding at the menopause age is at present as follows:

I. Determine operability of the patient

A. General:

Circulatory, excretory, respiratory  
Constitutional (obesity, senility)

B. Local

Technical (obesity, accessibility)  
Extent of disease

II. Determine acceptability of artificial menopause

III. In the operating room

A. Curettage of cervix (specimen)

B. Curettage of endometrium (specimen)

Precise determination of source of curettings

Specimens (1) in formalin for an 8-hour report

Specimens (2) in Zenkers (permanent preparation)

C. Radium is inserted as for carcinoma of corpus

IV. A. The 8-hour pathologic report is "benign": Radium remains for a dose of 2,400 mg. hr. (Sterilizing dose)

B. The 8-hour pathologic report is "malignant"

(1) The operative risk is slight

(a) Radium remains for a dose of 3,000-3,600 mg. hr.

(b) Complete abdominal hysterectomy 5 weeks later

(c) Roentgen therapy about one month later

(2) The operative risk is great or the disease extensive

(a) Radium remains for a dose of 5,000 mg. hr.

(b) Roentgen therapy about a month later

DR. THOMAS C. PEIGHTAL.—Worthy of note in this paper is the statement that such criteria as size of the uterus and presence or absence of pain are useful factors in clinically classifying and estimating prognosis in these growths. Also of interest is the fact that patients with Grades III and IV carcinomas did no better with hysterectomy than with radium alone. This paper rightly stresses the importance of a technique which aims, in so far as possible, to place the radium in contact with the entire uterine cavity, and which by spacing x-radiation, radiation and surgery sufficiently far apart thus avoids too great depletion of the patient's strength before the hysterectomy is done, a matter for careful consideration if the usual operative mortality in this elderly age group is not to be increased.

In checking over briefly the end results in 172 cases of corpus carcinoma on the Gynecological Service of the Roosevelt Hospital from 1910 to 1933 it is of interest to note that the five-year cure rate has definitely improved as more and more cases have had radiation in conjunction with hysterectomy. From 1910 to 1925 surgery alone was used almost uniformly, 80 per cent of cases were considered operable and the absolute five-year cure rate for the 90 cases of this period was only 26 per cent. From 1926 to 1929 some of the 49 cases admitted had radium and high voltage therapy either preoperatively or postoperatively. Of these, seven, well advanced, received radium alone and none lived five years while in the 42 with hysterectomy there was an absolute five-year cure rate (for the whole 49 cases) of 41 per cent. From 1930 to 1933 increasingly more cases were treated with radium alone plus high voltage therapy and more cases had prehysterectomy radiation. Of the 33 cases in this period 20 had hysterectomy and 13 received combined radiation only. The absolute five-year cure rate in these two groups (based on the total 33 cases) was 43 per cent and 23 per cent, respectively. In the past three years nearly all operable cases have received radiation in conjunction with hysterectomy, and we feel confident that the marked improvement in prognosis amply justifies the added time and inconvenience which proper preoperative radiation entails.

DR. NELSON B. SACKETT.—At the Woman's Hospital we have had 123 patients who have been followed five years or more, of which 115 were treated. Of that number, 56 are still alive, a five-year survival rate of 45.5 per cent absolute, and 48.7 per cent relative. I have studied our ten-year results in a small series of 30 cases, of whom 9, or 30 per cent, survived for ten years. If we add one patient who died after a strangulated hernia operation and who on autopsy showed no carcinoma, and another patient who died of apoplexy and in whom no carcinoma was found at autopsy, the ten-year survival rate is 36.6 per cent. We say "survival" even at ten years, because we have had two or three patients who survived ten years or more and who have since died of undoubted carcinoma.

We subscribe to Dr. Healy and Dr. Brown's conclusion that the combined therapy is best. Radiation alone gives us 34 per cent and the combined treatment gives 67 per cent, of five-year relative survivals. In operable cases, radiation alone gives a 45 per cent relative survival rate. Since at least one out of three hysterectomy specimens shows cancer persistent after radiation, the uterus should be removed whenever possible.

Our excellent results in cases of adenoma malignum make us wonder whether we are in this condition dealing with malignancy or not. Following one curettage in a recent case the pathologic diagnosis was adenoma malignum with some invasion of the stroma. A granulosa cell tumor had been removed by laparotomy at the time of this curettage. Six weeks later, a second curettage was done and the specimen showed almost complete obliteration of the marked glandular hyperplasia of the first specimen and no malignancy whatsoever. In a second case, I did a curettage and radium insertion for adenocarcinoma of the uterus, Grade III, with invasion of the uterine wall. This was followed later by panhysterectomy, and removal of a granulosa cell tumor. The uterus showed complete disappearance of the marked glandular hyperplasia found in the first specimen.

DR. W. P. HEALY.—One is amazed, if he studies the patients that come with carcinoma of the corpus and coincident pain but with no evidence of metastatic involvement, to find that these apparently favorable cases fail to survive for five years. Coincident involvement of the cervix in a case of primary cancer of the corpus is also of bad prognostic significance.

Since it gives such good end results, we have long thought that adenoacanthoma is just the result of metaplasia in adenoma malignum. Corpus cancers can be divided into two main groups, (1) the adenoma malignum type of case, in which the cancer occurs in bundles of glands piling up into the uterine cavity, and slowly invading the myometrium, but never breaking through the basement membrane, and (2) adenocarcinoma, which is the same type of growth plus free cancer cells in the stroma. There is a genuine difference in the prognosis of the two histologic groups.

I am inclined to believe, as Dr. Peightal remarked, that we might possibly omit hysterectomy in the Grade IV and embryonal types of cancer without disadvantage.

We have been much impressed with the fact that less than 3,300 millicurie or milligram hours of intracavitary radiation does not accomplish all one might hope for.

If you have a patient, in whom you are going to restrict treatment to irradiation methods, I would be inclined not to go above 3,600 millicurie hours with two, three or four capsules, according to the length of the canal, for the first treatment. Three months later, I would repeat the curettage and insert radium, in a small dose, we will say, of 2,000 hours. By all means add roentgen therapy, because one of the common forms of metastatic involvement in cancer of the corpus uteri is the lymphatic extension to the ovaries which will result in large ovarian tumors.

Radiation is a strain on these patients. I always tell the family that the patient is to undergo two major procedures. Irradiation is the first and it will, in my opinion, be fully six weeks after the last radiation treatment is given before she will be well enough to undergo hysterectomy. I find even that my tendency in the last year or more is to increase to eight weeks, instead of six weeks, the interval before hysterectomy is done.

In a considerable percentage of cases we find that there is little or no uterine cavity. There is instead a large mushy overgrowth of cancer, and no large cavity in which you can place capsules in various directions. For that reason we do not believe in trying to pack the uterine cavity with radon or radium tubes. Heyman admitted to me packing could not be done in every case, but, theoretically, he thought it a good thing to do if possible. Burnam, on the other hand, told me that he had given up this method and was simply using tandem applicators in the canal, as we do it at the Memorial.

We find that in about two out of three of our cases there is no evidence of cancer in the uterus when we take it out eight weeks after radium. On the other hand, since in one out of three there is residual tumor we must take the uterus out in all cases. This is also the reason why when we are going to treat a case with radiation only, three or four months after the first series of treatments with radium and x-ray, if the uterus remains heavy and large and if there is persistent uterine discharge, we re-investigate the interior of the uterus.

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Keller, R., and Limpach, J.: The Pre- and Postoperative Use of Transfusions of Placental Blood at the Strasbourg Maternity, *Gynéc. et obst.* 37: 173, 1938.

In view of difficulties in procuring donors, these writers resorted to the routine use of placental blood. An advantage of using this blood lies in the high content of erythrocytes, leucocytes, hemoglobin, and the presence of several hormones. The placental blood only of healthy, Wassermann-negative patients is used. A detailed description of the entire technique is given. Approximately 60 to 90 gm. (rarely 100 to 150) of blood are obtained at each birth.

When required the blood is heated to 38° by placing the flask in a water bath, then filtered through three thicknesses of sterile gauze into a sterile graduate that has been previously rinsed with physiologic saline.

The use of transfusions of placental blood in the treatment of the sickness following deep x-ray therapy has been efficacious, and it is enthusiastically recommended.

ARNOLD GOLDBERGER

## ERYTHROBLASTOSIS FETALIS AS A CAUSE OF FETAL MORTALITY\*

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*(From the Medical School of the University of Western Ontario)*

FOR some years it has been recognized that the condition known as hydrops fetalis is a cause of death in late fetal life, or immediately after birth. Fatal icterus of the newborn, as its name implies, is a cause of death shortly after birth and, judging from reports in the literature, is fortunately rather rare. In recent years these two conditions, together with some cases of congenital anemia, have been grouped under the heading of erythroblastosis fetalis, a condition in which the fetus or newborn child exhibits a marked degree of blood destruction and blood regeneration, which may be accompanied by any or all of the following: anemia, jaundice, general edema of the tissues and placenta, fluid in the body cavities, enlarged spleen and liver, yellow amniotic fluid and vernix caseosa. There is no general agreement among investigators as to whether the blood destruction is a primary factor, or whether it follows upon an abnormal type of blood production in which very early forms of the red and white cell series are found circulating in excess in the blood stream.

The histories of mothers giving birth to hydropic infants reveals an unusually high number of miscarriages, premature births, stillbirths, and births of macerated fetuses. Although this fact is noted, it has not been emphasized that these products of conception are probably examples of the same pathologic condition as are the outspoken cases of hydrops or icterus. Moreover, the possibility that many stillbirths or premature births of apparently normal infants in a family in which neither hydrops nor icterus has occurred, may be due to erythroblastosis has not received any attention. An article by Javert emphasizes that this condition is a potent cause of infant mortality, and points out that many infants who are apparently normal, but who die within the first two weeks of life without any evident jaundice or anemia, are really cases of erythroblastosis as revealed by autopsy. I wish to call attention to the probability that this disease is responsible for the death of an undetermined percentage of infants who are outwardly normal, and who are listed as stillbirths, in which there appears to be no obvious cause of death although occasionally perhaps there is difficult labor. If there is no history of hydropic or icteric infants in the family to call the attention of the obstetrician to the possibility of a definite pathologic basis for the stillbirth, an autopsy probably is not done, and the diagnosis is missed.

\*Presented by Charles C. Macklin, F.R.S.C., at a meeting of the Royal Society of Canada, Ottawa, Ont., May 27, 1938.

I wish here to report two diagnosed cases of erythroblastosis fetalis in stillborn infants, who were regarded as perfectly normal by the obstetrician and by the pathologist who examined them externally. In both cases the infant was definitely overweight, a fact which apparently should suggest the possibility of erythroblastosis, according to Javert. One was premature, one, full term. There was no evident jaundice in these infants; both were pale; one had hemorrhagic areas over the skin of the thighs and one had a scrotum tense with fluid, which collapsed when the abdominal cavity was opened. The placenta was not stated to be large in either case, and its size was mentioned as being normal in the case of the 14.5 pound infant. Both were regarded as victims of the hazards attending birth, delivery of the shoulders having been difficult in both cases. These two infants constituted two of the only three apparently normal full-term or almost full-term infants received into the embryology laboratory in a period of two years, inasmuch as the obviously defective ones are retained in the pathologic laboratory either for specimens, or for autopsy. That two of the three should prove definitely to be cases of erythroblastosis, suggests that an appreciable number of stillbirths at or near term that appear to be normal may be due, in fact, to erythroblastosis. Javert found this condition to be a more frequent cause of neonatal death than was syphilis.

CASE 1.—Baby C.\* The obstetric history of the mother was that she had had five previous pregnancies 18, 15, 13, 8, and 5 years before, all normal and going to full term. The largest child weighed 10.5 pounds at birth. The mother was very obese, weighing 238 pounds. The sixth pregnancy was terminated by induction of labor at eight and one-half months because of the size of the fetus, and the increasing blood pressure of the mother. The head was delivered with little difficulty, but the shoulders were so broad that they had to be delivered by means of a hook. The weight of the child, which was dead, was 14.5 pounds. There was no apparent edema of the placenta or of the infant except for the fluid in the scrotum previously referred to. The child was regarded as normal, death being due to difficult delivery. Dissection revealed a rather amazing picture. The organs were enlarged far more than would be expected even in a 14.5-pound child. As will be seen from Table I and Fig. 1 the organs were all above normal weight. The black column represents the relation of the weight of the organs of this fetus expressed in percentages of

TABLE I. WEIGHT OF ORGANS IN TWO CASES OF ERYTHROBLASTOSIS

	BABY C. 8.5 MO.	NORMAL†	BABY B. FULL TERM
Heart	66.0 gm.	17.0 gm.	35 gm.
Liver	1,120.0 gm.*	78.0 gm.	321 gm.
Spleen	20.0 gm.	8.0 gm.	18 gm.
Thymus	18.0 gm.	13.7 gm.	27 gm.
Lungs	79.0 gm.	39.0 gm.	100 gm.
Kidneys	36.5 gm.	27.0 gm.	43 gm.
Adrenals	23.5 gm.	5-6 for adult‡	33 gm.
Fetus	14.5 lb.	7.5 lb.	11 lb.

\*A piece of liver estimated as 1/10 to 1/7 of the entire liver, containing the entrance of the umbilical vein, weighed 160 gm. The remaining liver was discarded before its weight was ascertained.

†Normal weights taken from Mallory's *Pathological Technique*, 1938.

‡No weight for adrenals at birth was given.

\*I wish to express my thanks for this specimen and for the obstetrical history to Dr. Evan Shute of London, Ontario.



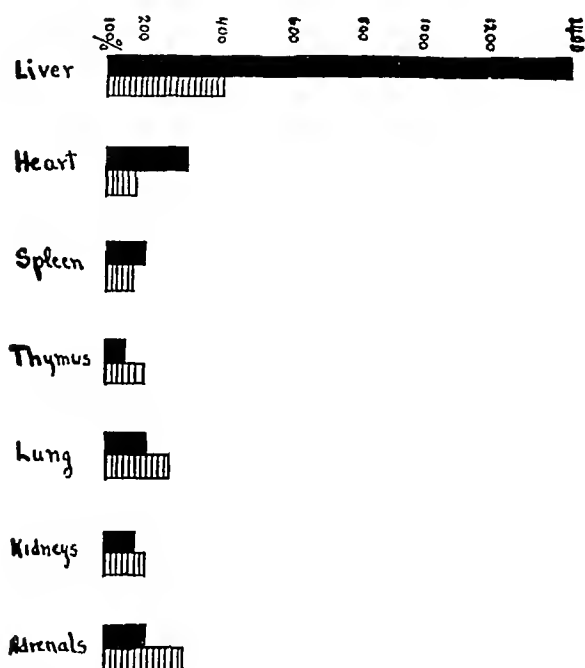


Fig. 1.—Weights of organs of two cases of erythroblastosis expressed as percentages of normal weights. The base line is taken in each case as 100 per cent of the normal weight of the organ in question. The solid black columns are the weights of the organs in Case 1; the lined columns those of the organs in Case 2.

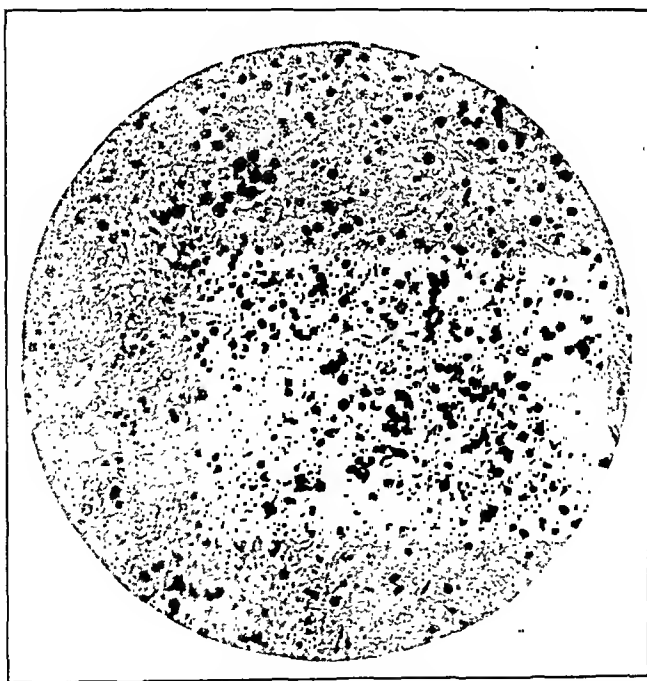


Fig. 2.—Section of liver of Case 1. Note the numerous areas of hemopoiesis, the crowding of the cords by the sinusoids filled with blood cells mature and immature, with a consequent loss of normal liver topography.  $\times 195$ .

the normal weight of the organs of the newborn, the base line being 100 per cent in each case. The lined column deals with the weight of the organs of the second case to be reported. Note that the liver was 14 times its normal weight, the heart nearly four times as heavy as normal; while spleen, lungs, and adrenals were approximately 200 per cent of their normal weight; thymus and kidneys being about 150 per cent of the normal weight.

*Liver.*—The liver was tremendously enlarged. The dissector who was preparing the fetus for embryologic demonstration threw away most of the liver, keeping only a narrow segment where the umbilical vein entered. This narrow slice, estimated variously as about one-tenth to one-seventh of the entire liver, weighed 160 gm. The liver would have weighed then according to the most conservative estimate at least 1,120 gm. Areas of hemopoiesis were far more numerous than in the normal



Fig. 3.

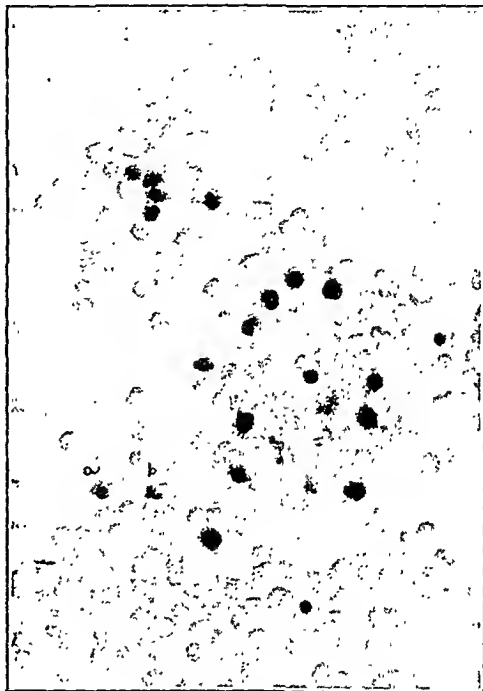


Fig. 4.

Fig. 3.—Section of a full-term fetal liver as control. Although areas of hemopoiesis are present, they do not crowd the sinusoids, and the normal liver pattern is apparent.  $\times 400$ .

Fig. 4.—Blood smear from 8.5 months' fetus with erythroblastosis fetalis (Case 1). As the blood had clotted, it was impossible to make a good smear. The stem cells and nucleated reds tend to clump in a thick mass, one of which is seen in the center of the field; hence parts of it are out of focus. *a* and *b* are two nucleated red cells, *a* with a single large nucleus, *b* with a nucleus fragmented into three parts. There is a wide variation in size among the red cells.  $\times 400$ .

liver. Fig. 2 shows the section of liver of this fetus, with many areas of blood formation, most of the nucleated cells being of the red series. The sinusoids were crowded with blood cells, and the liver cords were so compressed by blood as to be almost unrecognizable. The contrast between this and a picture of the liver from a full-term normal fetus, in which the liver cords are well defined, the cell boundaries clear, and only occasional areas of blood formation are present, is brought out in Fig. 3. Seventy per cent of the nucleated cells in the blood stream in the liver were nucleated red cells. Only 2 per cent of the nucleated cells in the circulation were mature white blood cells, the remaining 28 per cent being immature stem cells, mostly of the erythrocyte series. Fig. 4 shows a field of blood from this fetus. Because the blood was not fresh when the smear was made, it is poor as a smear, but shows a group of nucleated red cells. These tend to clump together. The variation in size is well shown in this smear.

Evidences of blood destruction were found in the masses of bile pigment which crowded the cells and capillaries, not only of the liver, spleen, adrenals, and kidneys but also of the lungs. These are seen as small black dots in Fig. 2. No iron was found in the cells by the Prussian blue method. This baby, had it lived, would doubtless have developed either fatal icterus, from which it would probably have succumbed, or congenital anemia.

Because this baby showed no iron in the liver, it might be denied inclusion into the category of erythroblastosis by those who insist that only those cases showing hemosiderin in the liver cells be included in this classification. Ferguson has described cases of erythroblastosis without jaundice, or edema, and which contained bile pigment but no iron in the liver cells.

*Heart.*—The heart weighed 66 gm., almost four times the normal weight. The left ventricular wall, usually thinner than the right in the fetus, was as thick as the right; and both were much hypertrophied, being 11 mm. in thickness. The thickness of the ventricular walls in the adult are given by Delafield and Prudden as 0.4 to 0.6 cm. for the right ventricle, and 1.6 cm. for the left. In this infant, the hypertrophy of the right ventricle was due to a stenosis in the ductus arteriosus; that of the left apparently was due to the impediment offered to the blood flow by the erythroblastic foci in the capillaries of the different organs. There was scarcely any lumen in the left ventricle, so hypertrophied were the walls.

*Spleen.*—The spleen which weighed 20 gm. showed areas of erythroblastosis. Although the lymphoid follicles are not thought to be as prominent as usual in cases of erythroblastosis fetalis, there were definite large follicles about the arteries in this spleen. The congestion was so marked that little of the normal architecture of the spleen, apart from the lymphoid follicles, was evident; the sinusoids being so distended with red blood cells and erythropoietic foci as to leave little of the splenic cells visible. Bile pigment, free and in cells, was abundant.

*Kidneys.*—These weighed 38.5 gm.; the blood vessels were dilated and filled with blood cells. In the capillaries, these were packed tightly, and had not taken up the stain although in nearby large blood vessels, the red cells were brilliantly colored. The explanation of this is not clear; the discs appeared as mere ghostly forms devoid of all hemoglobin content. The outermost zone of the medulla and the glomeruli were rich in hemopoietic foci; the intracapsular space being crowded with immature forms with dense nuclei and little cytoplasm. Bile pigment was abundant.

*Adrenals.*—The adrenals which weighed 23.5 gm. showed some congestion. There was bile pigment in the cells and in the capillaries, especially of the zona fasciculata. Extrahepatic formation of bile pigment was apparently going on in this fetus, with deposition of bile pigment throughout the organs. Most of the tissue especially of the zona fasciculata was degenerate, the remaining cells were large and brilliantly stained with the eosin.

Here then is a case in which there is erythroblastosis, in which there is hypertrophy of heart, liver, and spleen, in which there is excess production of bile pigments but in which there is no evidence of iron in the liver cells. Jaundice would probably have occurred after birth when the burden of increased blood destruction normal to the newborn was thrown upon liver cells already compressed and filled with bile pigments.

*Brain.*—The brain showed marked congestion of the superficial vessels but no hemorrhages. There was no evidence of bile staining in any of the brain tissue, when examined in slices about 5 mm. in thickness.

**CASE 2.**—Baby B. This case was the next outwardly normal fetus at or near full term brought to the embryology laboratory. The obstetric history of the mother is as follows: Full-term child, now 17 years old. Second pregnancy, a stillbirth. Third and fourth pregnancies, normal full-term children alive and well. Fifth pregnancy a miscarriage. Sixth, a normal full-term child. Seventh a miscarriage. Eighth, stillbirth at term, subject of this report. Weight at birth 11 pounds. The baby was pale, and the skin had hemorrhagic spots over the arms and legs. It appeared normal, except for the pallor and the size. I suspected, with the history

of miscarriages and stillbirths, and the large size of this baby, that it too might be a case of erythroblastosis. At autopsy, the organs were enlarged, as shown by Fig. 1 and Table I. The relative weights of the organs of this infant compared with the normal as 100 per cent are shown in the horizontally lined columns. The liver in particular is over-weight. The thymus and lungs both had petechial hemorrhages over the surface, and weighed far more than normal. The brain of this infant as in Case 1 showed marked congestion of the superficial vessels; but no evidence of intracranial hemorrhage or of icterus. The organs showed excessive erythropoiesis.

*Liver.*—The liver which weighed 321 gm. showed great congestion, the sinusoids being blocked in many cases by hemopoietic areas as well as by mature red blood cells. The liver cords were compressed by these distended sinusoids until almost all semblance of liver was lost (Fig. 5). The periportal spaces were crowded with young blood cells. The liver cells themselves were large and coarsely granular.

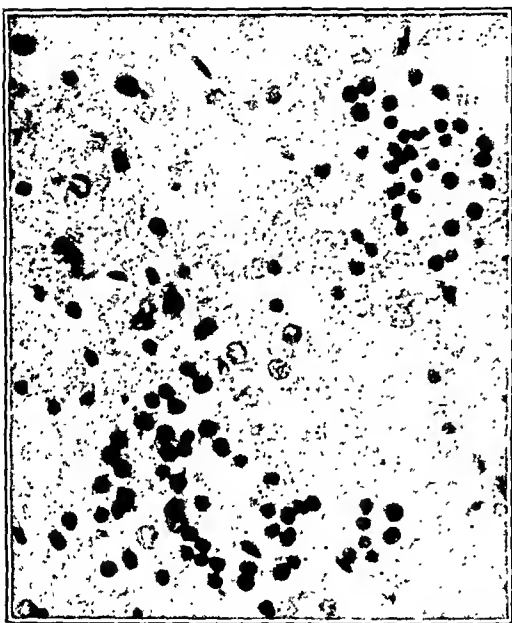


Fig. 5.



Fig. 6.

Fig. 5.—Liver of a full-term fetus with erythroblastosis fetalis (Case 2). Note the prominent areas of hemopoiesis, the loss of liver architecture through compression of the liver cords by red blood cells and hemopoietic areas in the sinusoids. Compare with Fig. 3.  $\times 400$ .

Fig. 6.—Blood smear from a full-term fetus with erythroblastosis fetalis. Note the small number of erythrocytes, and the great profusion of nucleated cells, most of which are immature cells of the granulocytic series.  $\times 400$ .

In some areas the cytoplasm was practically gone, the only occupant of the cell being the nucleus which was as large as 18 micra across. There was a large amount of bile pigment in the hepatic cells as well as free in the blood vessels. No iron was found in the hepatic cells when they were treated by means of the Prussian blue reaction. This was also true of all the organs examined.

*Blood.*—In areas of hemopoiesis many of the nucleated blood cells possessed a cytoplasm which stained like that of mature red blood cells. Other cells, smaller than those with dense nuclei, and very little protoplasm, suggested stem cells. Immature white blood cells were found in the blood vessels. Of 374 cells found within the blood vessels in the liver, 38, or 10 per cent, were nucleated. In a count of 120 nucleated cells, 60, or 50 per cent, were definitely nucleated reds, and 19, or 16 per cent, were mature white blood cells. The remaining nucleated forms were either the primitive stem cells, or myeloblasts. Fig. 6 shows an area from a blood smear which is composed of red cells and a group of myeloblasts. Because of the fact that the

blood was not obtained until eighteen hours after death, the smear is poor. Here there are far more nucleated than nonnucleated cells. The estimate of the percentage of cells which were nucleated was made from cells in a blood vessel rather than from the smear because of the uneven distribution of cells in the latter.

Numerous red blood cells were found with large holes in them as if the nuclei had just been extruded. The cells varied markedly in shape as well as in size, ranging from  $4\frac{1}{2}$  to 9 micra. White blood cells, rather rare in the mature form, varied from 6.8 to 12.9 micra. Platelets were extremely rare which might account for the hemorrhagic tendencies noted in these children.

*Heart.*—The heart weighed 35 gm. The heart cells, as well as the blood vessels, had an abundance of bile pigment in them.

*Spleen.*—The spleen weighed 18 gm. The lymphoid follicles were quite definite. Bile pigment was noted in the cells and free in the blood vessels. The endothelial lining of the capillaries and blood vessels were unusually prominent, forming a quite thick layer. Frequent megakaryocytes were seen.

*Adrenal.*—The adrenals weighed 33 gm., were extremely friable, so that it was almost impossible to pick them up. The adrenal sinusoids were packed with blood. The zona fasciculata was filled with huge eosinophilic cells whose lightly staining nuclei possessed a thin chromatin network. These eosinophiles grew more frequent in the reticular layer and the medulla where they, together with huge sinusoids, filled the latter structure. These cells averaged  $33\frac{1}{2}$  micra in diameter. Throughout the adrenal there were areas of hemopoiesis, and also areas in which bile pigments were abundant.

*Pancreas.*—The pancreas showed no areas of marked blood formation and some amount of bile pigment. The Prussian blue reaction was negative.

*Kidneys.*—The kidneys weighed 43 gm. Their glomeruli were filled with dark nucleated cells as was true in the first case. In some areas there were very large eosinophilic cells in the convoluted tubules which stood out with unusual distinctness.

Here then were two fetuses, which were definite cases of erythroblastosis fetalis, with no outward sign of abnormality except undue size and that the fetus was supposed to have died in each instance due to prolonged delivery because of this. It may indeed have been a factor, but inasmuch as erythroblastosis is known to cause death when accompanied before birth by hydrops, and after birth by jaundice, even in normal-sized infants, it is not unreasonable to suppose that this was the primary factor in causing fetal death in these cases. It is impossible to say how many stillbirths of infants at or near term can be attributed to this condition until some large obstetric clinic routinely examines at autopsy all products of conception. Javert suggests that all infants weighing over 1,500 grams who die in the first two weeks of life be examined at autopsy for this condition, he having found 4.5 per cent so affected in a series of 110 such cases. I would suggest that *all* fetuses within the viable period that are born dead or succumb shortly after birth be examined for the presence of erythroblastosis whether they be outwardly normal or not, in order still further to ascertain the importance of this condition in causing the death of infants either before or during birth; also, in families in which there is no evidence of syphilis, or any cause for repeated miscarriage that products of conception born before the viable period be examined in order to determine how early in fetal life this condition may arise.

Transfusion is helpful in these cases, and it is possible that where the obstetrician has cause to suspect that the infant may have erythroblastosis because of a family history of the condition, early induction of labor while the fetus is still viable, followed by immediate trans-

fusion may reduce the mortality of this group of infants. It is not improbable that the obstetrician has frequently received blame for poor management of a case because the child was born dead, when in reality, the blame should have been placed on the pathologic condition from which the child suffered.

I have suggested (1937) that erythroblastosis is due to a dominant mutation in one of the primitive germ cells of one of the parents, and that all subsequent germ cells derived from this original one would possess the mutated gene, so that approximately half the children would be affected in a series of families in which this occurs. Darrow (1938) has stated that she believes it to be due to a sensitization of the mother to fetal hemoglobin during a pregnancy, through the escape of fetal blood into the maternal blood stream, with a subsequent hemolysis of the fetal blood as the antibodies pass back through the placenta into the fetal circulation. She states that this explains the fact that all children born after the time when the first one develops erythroblastosis will have the same condition, as the mother retains the antibodies which cause hemolysis of the fetal blood. The obstetric history in the second case is not in agreement with such a theory, inasmuch as several normal children were interspersed between the stillbirths and miscarriages in this family. It is true that the others were not proved cases of erythroblastosis, but in these families it is probable as Darrow admits, that all miscarriages and stillbirths are to be regarded as evidences of this condition.

I have reviewed much of the literature dealing with cases of erythroblastosis and have found that there are enough families reported in which normal children followed the child with erythroblastosis to make it apparent that the rule which Darrow calls attention to is by no means infallibly followed; namely, that once a child in a family has exhibited this condition all subsequent children will be affected. There are a few records of twins born, one normal, one affected, which also make it questionable whether Darrow's explanation can hold in all instances, for circulating antibodies in the mother's blood stream should affect both twins equally. Table II lists cases in which normal children followed the birth of one with icterus gravis or hydrops, and some, such as Cohn's in which normal children were interspersed between two hydropic infants, so that the criticism cannot hold here, that perhaps the antibodies in the mother's blood had lost their potency and so enabled a normal child to be born after the first one with hydrops. Table III gives the instances in which twins were born, one said to be normal, the other affected.

It is true that in some of the cases listed in Table II, the diagnosis was not confirmed by autopsy, and so it might be objected that the cases may not have been true erythroblastosis fetalis. The family history of miscarriages, stillbirths, infants dying within a few days of jaundice or with convulsions and with no evidence of syphilis is one that so far has not been duplicated in other conditions hence such an extensive history is reliable evidence, in most instances, of erythroblastosis fetalis especially when the disease is outspoken in one of the later children in the family.

TABLE II

AUTHOR	ORDER OF BIRTH	REMARKS
Abt	<ol style="list-style-type: none"> <li>1. Died 3rd day of jaundice</li> <li>2. Eight months stillbirth</li> <li>3. Died pneumonia twelfth day</li> <li>4. Died fourth day of jaundice</li> <li>5. <i>Normal male</i></li> <li>6. Jaundice, transfused, recovered</li> <li>7. Premature, jaundiced, died on second day</li> </ol>	
Astrachan	<ol style="list-style-type: none"> <li>1. Intense jaundice, recovered, died 2 months, with paralysis</li> <li>2. Died fifth day of jaundice</li> <li>3. <i>Normal male aged 10 years</i></li> <li>4. Died fourth day jaundice</li> <li>5. Died on third day jaundice</li> <li>6. Jaundice, given maternal serum, recovered</li> </ol>	<p>Probably cerebral symptoms due to lesions occasioned by jaundice</p> <p>Pathologic picture of erythroblastosis fetalis</p> <p>Same pathologic picture</p>
Ritter cited by Ballantyne	<ol style="list-style-type: none"> <li>1, 2, 3. <i>Normal</i></li> <li>4. Child with hydrocephalus and large placenta</li> <li>5. <i>Normal</i></li> <li>6. Hydrops</li> </ol>	Large placenta suggests presence of erythroblastosis
Löhlein cited by Ballantyne	<ol style="list-style-type: none"> <li>1. <i>Normal</i>, died 4 years meningitis</li> <li>2. Died of fits at 6 mo.</li> <li>3. Died early of general weakness</li> <li>4. Premature, 36 weeks, hydrops</li> <li>5. <i>Normal infant</i></li> </ol>	Suggestive of cerebral symptoms of kernicterus
Broekwell	<ol style="list-style-type: none"> <li>1. <i>Normal</i></li> <li>2-9. Two were miscarriages, six were jaundiced, of whom one died</li> <li>10. <i>Normal</i></li> </ol>	
Cohn cited by Ballantyne	<ol style="list-style-type: none"> <li>1-5. Miscarriages</li> <li>6. Hydrops</li> <li>7. <i>Normal</i></li> <li>8, 9. Hydrops</li> </ol>	
Diamond and others	<ol style="list-style-type: none"> <li>1, 2. <i>Normal</i></li> <li>3. Anemia, jaundice, transfused, recovered</li> <li>4. <i>Normal</i></li> <li>1. Died of jaundice first day</li> <li>2. Jaundice, anemia, transfused, recovery</li> <li>3. <i>Normal</i></li> </ol>	
Dorff and Shapiro	<ol style="list-style-type: none"> <li>1. Died with erythroblastosis fetalis at 1 day</li> <li>2. <i>Normal</i> as far as this condition is concerned</li> </ol>	

TABLE II—CONT'D

AUTHOR	ORDER OF BIRTH	REMARKS
Fordyce and McAfee	1. Normal male 2. Died 2 months of jaundice 3. Died first day of jaundice 4. <i>Normal male</i>	
Hampson	1. Normal male 2-9. Died before 3 days jaundice 10. <i>Normal female</i> 11-14. Died before 3 days 15. Jaundiced, recovered 1-7. Died of jaundice 8-10. Miscarriages 11-13. <i>Living and well</i>	
Hawksley	1-3. Normal 4. Stillbirth 5. Died 2 months jaundice 6. <i>Normal</i> 1. Jaundice male died 3 months 2. Miscarriage 3. <i>Normal</i>	Last 3 of 13 pregnancies normal Bile ducts were patent
Hellman and Hertig	1. Normal 2. Hydrops 3. <i>Normal</i> 1, 2. Normal 3, 4. Miscarriages at 6 weeks 5, 6. <i>Normal</i> 7. Hydropic female 8. Ectopic pregnancy 9. <i>Normal</i> , alive and well 1, 2, 3. Normal 4. Hydrops 5. <i>Normal</i> 1. Normal 2. Died 3 months of convulsions 3, 4, 5. <i>Normal</i> 6. Died fourth day of jaundice 1. Normal 2. Died second day jaundice 3. <i>Normal</i> 1-5. Normal 6. Jaundice, erythroblastosis 7. <i>Normal</i>	Born 1 year after hydropic fetus In view of later family history, may have been case of kernicterus Recovered after transfusions
Jakesch cited by v. Gierke	1-5. Normal 6. Hydrops 7. <i>Normal</i>	Placenta 3 times as heavy as normal
King	1, 2, 3. Normal 4. Died third day of jaundice 5. Eight months macerated fetus 6, 7. Miscarriages at 4 months 8. <i>Normal and well</i> 9. Died eighth day jaundice and convulsions 10. Macerated fetus 11. Hydrops 12. Macerated fetus	



TABLE II—CONT'D

AUTHOR	ORDER OF BIRTH	REMARKS
Lockwood	1. Died at birth, cause unknown 2. <i>Normal</i> 3. Hydrops	Baby was very large, probable case of erythroblastosis
Mackay	1. <i>Normal</i> 2. Miscarriage at 5 months 3. Died tenth day jaundice 4. <i>Normal</i> 5. <i>Normal</i> 6. Died 3 weeks jaundice 7. Died twenty-seventh day jaundice 8. <i>Normal</i>	
MacWatters cited by King Mannheimer	1. Hydrops 2, 3, 4. <i>Normal</i> 1. Congenital anemia	Large liver and spleen, 63,800 W.B.C. 24 erythroblasts per 100 W.B.C.
	2, 3, 4. <i>Normal</i>	
Nason	1, 2. <i>Normal</i> 3. Miscarriage 4-7. Jaundiced. Died except seventh child who recovered  8. Died diarrhea 9. Stillbirth 10, 11. <i>Normal</i>	Mother jaundiced also from fourth to eighth pregnancies. History not like that of acholuric jaundice where children are not so ill, and do not usually die in infancy of the disease
Pasachoff	1, 2, 3. Erythroblastosis fetalis	
Rautmann	4. <i>Normal</i>  1. <i>Normal</i> 2. Stillbirth, 7 months 3. Died third week, intestinal catarrh 4, 5. <i>Normal</i> 6. Hydrops	Mother treated during fourth pregnancy, but does not say how  Probable case of erythroblastosis fetalis
Taylor	1-4. <i>Normal</i>  5. Miscarriage 6, 7, 8. Died in few days of jaundice 9. <i>Premature but healthy and survived</i> 10. Died seventh day of jaundice	Several of mother's sisters died in infancy of jaundice and convulsions. May be thought to be acholuric, but in such families infant death and convulsions rare

TABLE III. FAMILIES IN WHICH ONE TWIN HAD ERYTHROBLASTOSIS FETALIS, OTHER NORMAL

AUTHOR	HISTORY	REMARKS
Andrews	1, 2, 3, 4. Normal 5. Eight months fetus 6. Twins. Normal female. Hydropic male	Both twins died, one at birth, the other 4 hours later. Question as to whether female twin was also affected, but its placenta was normal, while that of hydropic twin was "enormous"
Bushnell and Aldrich	1. Normal 2. Died eleventh day, enlarged thymus 3. Full-term stillbirth 4, 5. Spontaneous miscarriages 6. Twins, fraternal. Female affected. Other normal	Jaundice at 2 days, transfused many times, lived. Developed cerebral symptoms at 6 mo. Died at 13 months
Lynch	1. Normal but died in few hours 2. Twins, said to be monovular because placenta was "single." One normal female, one hydropic female	Liver of affected twin showed "round cell infiltration" (probably hemopoietic areas with many early forms). Also brown bile pigment clumps in cells
Oberndorfer cited by Peters	Twins. One wholly normal. One hydrops	
Wooley	Twins. One normal. One hydrops	Delay in birth of normal twin caused by prolonged delivery of hydropic twin caused death of normal infant. No autopsy on normal twin, therefore latent erythroblastosis not excluded
Capon	1. Miscarriage at third month 2. Stillbirth 3. Twins. Normal female. Hydropic female	Both died, organs of normal twin much heavier than normal and would suggest that although outwardly normal, this twin was also a case of erythroblastosis fetalis

Families in which normal infants are interspersed between miscarriages and stillbirths before they finally end in the production of an hydropic infant are also included here because of the fact that these products of conception are regarded as evidences of the disease. There is evidence then, that Darrow's interpretation does not fit all the cases.

Other observations, not in agreement with Darrow's views, are as follows: She points out that Hampson's use of repeated small doses of the mother's serum in effecting a cure in these children might be regarded as a desensitization process, but Greenwald states that the experience of others does not confirm Hampson's work. Moreover some

of the best results obtained with these children have been secured by transfusions with the mother's whole blood (Diamond, Blackfan and Baty). This work makes one query why giving mother's blood which supposedly has the hemolyzing factor for the infant's hemoglobin in it, should stop the hemolysis and allow the child to recover; also why the condition should progress rather than regress once the child is born, unless in some cases the placenta is impermeable, while the breast secretes the antibodies.

More research is needed on this problem, and one of the contributions must be the determination of the normal development of the hemopoietic system at all stages of fetal life, and the determination of how early the excess hemopoiesis may be detected in cases of miscarriages in families whose earlier history has suggested the probability of erythroblastosis fetalis. Darrow's ideas as to the sensitization of the mother to fetal hemoglobin should be further investigated. When we have a more accurate estimate as to the frequency of this condition, and how often so-called "premature" infants die, not of prematurity but of erythroblastosis, we may judge more adequately the truth of the statements that maternal age plays a role in the etiology of this condition, and that the affected children tend to come at the end of the childbearing period. How many infants with this condition have died who were born in the early years of the mother's obstetric history, and who were not diagnosed properly because the fetus was not examined, we do not yet know.

#### SUMMARY

Two and possibly three cases of erythroblastosis fetalis are described. They were the only outwardly normal full-term or near full-term infants received in the embryology laboratory, and two of the three were found to be cases of erythroblastosis fetalis when examined at autopsy, although the infants had been regarded as normal by the obstetrician. It is suggested that this condition may be a cause of many stillbirths at or near term, and of many deaths formerly attributed to prematurity and it may go unrecognized because it does not always cause external manifestations, such as hydrops or jaundice. The obstetrician may receive blame for mismanagement of the case because of the death of the infant. The lives of some of these children might be saved by induction of labor while the fetus is still viable, followed by transfusion, if the obstetrician is aware that the mother has given birth to other offspring with erythroblastosis. Such knowledge will be gained only by subjecting all stillbirths, premature infants and outwardly normal full-term infants, dying immediately after birth, to routine pathologic inspection. Just as "senility" has given way to a more adequate classification in most cases, so "stillbirths" and "prematurity" will give way to more accurate cataloguing as the causes of death are more scientifically determined.

I desire to express my deep gratitude to Prof. Chas. C. Maeklin, who suggested the dissection of these fetuses for this study, and who generously assisted in the interpretation of the histologic sections as well as assistance in the photomicrographs; I also wish to thank Mr. Walter Downs for his assistance in the photomicrographs.

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## THE UNSTRIATED MUSCLE FIBER OF THE FEMALE PELVIS

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THE problem of the mechanics of the uterine supports has attracted the attention of investigators for the past century. The early workers devoted themselves to the anatomy of the "ligamentous supports of the uterus." They assumed that the uterine ligaments were in purely fibrous structures, and it was not until 1888, when Ziegenspeck and Winkel demonstrated the presence of smooth muscle in the base of the broad ligament, that a possible muscular support for the uterus, other than that provided by the levator ani, was conceived.

Since 1891 many workers have drawn attention to the fascial constituents of the pelvic floor and the relation of these to the blood vessels and nerves.

Maackenrodt (1895), summarizing previous work on the constituents of the tissue at the base of the broad ligament and adding his own observations, concluded that smooth muscle fibers extending laterally from the cervix uteri are found constantly in this region. Tweedy (1911 to 1916) considered that these fibers are attached laterally to the endopelvic fascia along the "white line." It is interesting to note that Thompson (1901) attributed the "white line" to a "condition of strain." It is possible that this strain is provided by the pull of these fibromuscular bands. Moritz (1913) denied the existence of separate "ligaments of Maackenrodt" but maintained that they were simply "pelvic areolar tissue" strengthened by perivascular sheaths. He admitted, however, that smooth muscle surrounded the vessels and nerves which form the vascular pedicle of the uterus. It is not a matter of great moment whether the smooth muscle of the pelvis is associated with vessels and

nerves, or whether it is an independent sheet, provided it is admitted that there are such muscular fasciculi attached to the cervix. The uterosacral and round ligaments have long been shown to contain masses of smooth muscle.

Smooth muscle originating in the uterus passes into the uterosacral ligaments. The round ligaments are largely muscular, though receiving considerable connective tissue support from the attached peritoneum. Bovee regarded them as having a strong influence in maintaining the uterus in a forward position. According to Nyulasy (1921), the cardinal ligaments or ligaments of Mackenrodt consist of three fibromuscular "heads." The superior "head" is associated with the transverse; the middle "head" with the ascending part of the uterine artery; while the inferior "head" arises from the lateral vaginal fornix. The three "heads" are then inserted into the posterior layer of the broad ligament. He notes that the three "heads" are best seen at full-term pregnancy. Smaller bands of smooth muscle have been recognized in the rectovesical and vesicovaginal septa. Goff (1931) described the areolar connective tissue in the rectovaginal and in the vesicovaginal septa, and disclosed its smooth muscle content. His sections taken at various levels were from a well-developed nullipara. Testu (1902) showed that the round ligament is composed of smooth muscle rich in elastic tissue.

The literature upon the fascial supports of the uterus deals chiefly with the surgical aspects. In most of these references there is a considerable lack of precision in the descriptions of the anatomy of the parametrium and of its constituents. In order to obtain accurate observations of the actual origin and insertion of all these "bands," "fasciculi," "heads," and "ligaments," serial sections were prepared of fetal female pelvises cut in transverse and sagittal planes. By tracing the course of these muscular tissues which converge upon the uterine cervix, it was possible to reconstruct the whole of this "smooth muscle diaphragm" and to formulate some of its functions.

The first part of this paper contains a summary of the observations which have been made. In the discussion which follows the functional aspect and the surgical anatomy of the smooth muscle tissue are described. Materials and Technique: The material consisted of transverse sections of 1 six and 1 seven months' fetus, and of sagittal sections of a seven and one-half months' fetus; and dissections of the pelvis of one full-term fetus; 10 adult pelvises and 1 *Macacus rhesus* pelvis. The specimens were prepared by the injection of the abdominal aorta with 10 per cent formalin. After allowing twenty-four to forty-eight hours for hardening, the pelvic contents were removed in a solid block complete with the levator ani and obturator internus muscles. The blocks were embedded in paraffin and sectioned at either 10 or 15 microns. The slides were stained with Ehrlich's hematoxylin and counterstained by the Van Gieson method. Numerous serial drawings were made and prepared on glass slides, but owing to the minute size of some of the muscular bands, these proved to be difficult to interpret, and consequently are not referred to in this text. It was only by tracing individual bundles through the series and by comparing the transverse and sagittal sections that an accurate picture was obtained. The reconstruction of the muscular bands was done schematically in the several drawings, reproduced here, but the course of each fascicle of

muscle tissue is demonstrated by photomicrographs of the actual sections taken at a uniform magnification of 16.8 diameters except in Fig. 7, where the magnification was 6 diameters.

### OBSERVATIONS

The smooth muscle tissue, lying between the pelvic peritoneum and the upper or superior surface of the levator ani muscle, is arranged as a series of bundles radiating from the uterus at the level of the internal os. The peripheral attachments of these bundles enable the tissue to be divided into three groups of fibers: anterior, lateral, and posterior groups.

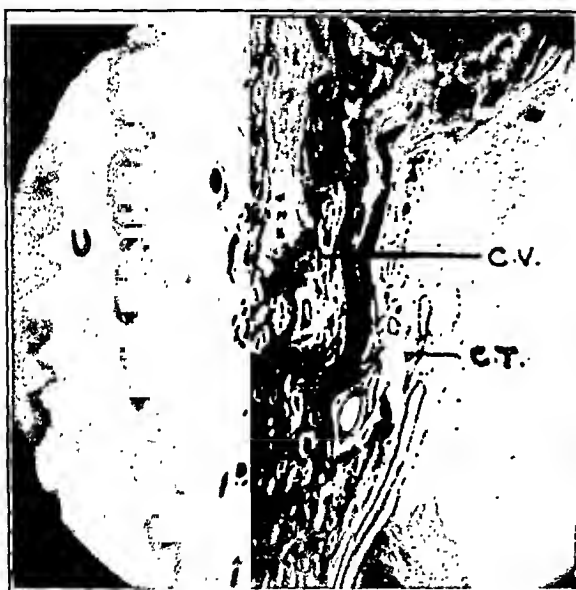


Fig. 1.

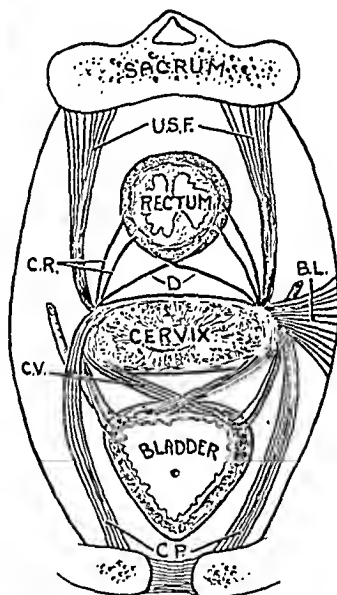


Fig. 2.

Fig. 1.—*U.*, uterus; *C.V.*, cervicovesical fibers; *C.T.*, connective tissue.

Fig. 2.—*C.P.*, cervicopubic bundle; *C.V.*, cervicovesical fibers (decussating); *C.R.*, cervicorectal fibers; *D.*, decussation; *B.L.*, broad ligament (lower bundle); *U.S.F.*, uterosacral fibers.

The *anterior fibers* arise from the anterior and the anterolateral aspect of the cervix and are attached (a) to the posterior aspect of the os pubis either directly or through the intermediary of fibrous bands and (b) into the muscular coat of the bladder. The muscle fibers which make up this group can be subdivided into the following bundles:

a. *The cervicovesical bundles:* (Figs. 1 and 3). These pass as a thick bundle of fibers from the cervix at the level of the internal os, converge toward the median sagittal plane, and intermingle with the circular and longitudinal coats of the bladder musculature. They terminate at the base of the bladder in the trigonal muscle. Beneath these muscular fibers is a connective tissue stratum directed toward the os pubis. Between these two structures numerous veins are seen. In the fetus, the bladder and pelvic viscera being abdominal organs, the upward obliquity of the smooth muscle fibers is very pronounced.

b. *The cervicopubic bundle:* (Figs. 1 and 2). From the level of the internal os passing upward toward the posterior surface of the os pubis, there pass many bundles of muscle tissue which are longer than the cervicovesical masses. They pass alongside of and beneath the base of the bladder and end either directly on the os pubis

or insert themselves into the fascia covering the bone. Beneath this bundle lies a layer of connective tissue which radiates from the cervix to the posterior surface of the os pubis. This is the same layer that was described in relation to the cervico-vesical bundles.



Fig. 3.—*B.*, bladder; *U.R.*, ureter; *V.V.*, vesicovaginal septum; *V.W.*, vaginal wall.



Fig. 4.—*V.*, vagina; *A.F.*, anterior fornix; *C.V.*, cervicovaginal fibers.

*c. The vesicovaginal bundle:* (Figs. 2, 3 and 10). In the vesicovaginal septum, smooth muscle fibers pass medially from the lateral vesicovaginal junction into the vesicovaginal septum, where they decussate. Near the junction of the posterior wall of the urethra and the anterior vaginal wall they are quite pronounced. At a lower level where the base of the bladder is in contact with the vaginal wall, these fibers are less numerous, and a loose avascular areolar connective tissue stratum is present (Fig. 3). At the lateral vesicovaginal junction condensations of smooth muscle are present in whose meshes nerve ganglia and vessels are seen.

d. *The cervicovaginal bundle:* (Fig. 4). Short fibers pass from the cervix slightly below the level of the internal os and pass to the musculature of the anterior vaginal fornix.

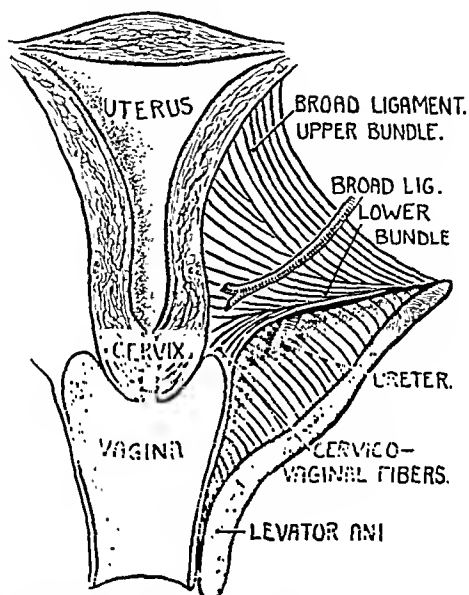


Fig. 5.—Schematic representation of smooth muscle fibers in the broad ligament representing upper bundle, lower bundle, and cervicovaginal fibers.

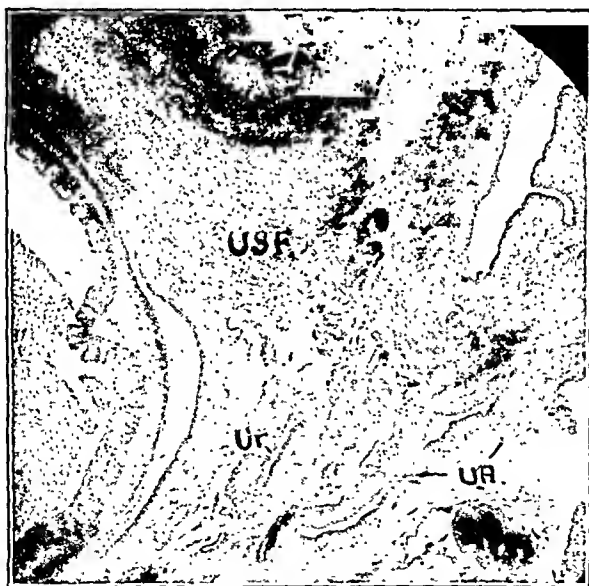


Fig. 6.—U.S.F., uterosacral fibers; U.R., ureter; U.A., uterine artery.

*The Lateral Group.*—The lateral group (which is apparently identical with the ligaments of Mackenrodt) arises similarly from the lateral aspect of the cervix. They diverge and form a flattened fan of fibers which is attached by means of fibrous strands to the "arcus tendineus." This group is subdivided into an upper and lower bundle.

a. *The upper bundle:* (Fig. 5). The fibers which make up this bundle are short and radiate from the upper lateral uterine wall. They pass in an oblique and caudal direction, terminating in the subperitoneal connective tissue.



b. *The lower bundle:* (Figs. 3 and 5). These fibers originate slightly above the level of the internal os, and course in a lateral direction to terminate at the "arcus tendineus." This bundle of fibers contains the transverse portion of the uterine artery and passes above the ureter. Many nerve ganglia belonging to the inferior hypogastric plexus are surrounded by its fibers. From slightly below the level of the internal os fibers pass to the lateral vaginal fornix. Beneath the lower bundle



Fig. 7.—Rectal fibers and rectovaginal septal fibers. *C.R.*, cervicorectal fibers.



Fig. 8.—Posterior vaginal fornix fibers. *P.F.*, posterior fornix; *C.*, cervix; *C.Vag.*, cervicovaginal fibers.

there is a stratum of areolar connective tissue, radiating from the cervix to the "white line" and to the superior layer of fascia of the levator ani muscle. In the upper medial part of this areolar connective tissue, lateral to the vaginal fornix, the ureter passes on its way to the bladder.

*The Posterior Group.*—(Fig. 2.) Also arising from the cervix enter into the composition of the uterosacral ligaments or find insertion into the rectal walls, and recto-vaginal septum.

a. *Uterosacral fibers:* From the posterior-lateral aspect of the cervix, these at the level of the internal os, fibers pass posterolaterally beneath the peritoneum which forms the superior lateral boundary of the pouch of Douglas, and these fibers are lost in the presacral fascia over the second and third sacral vertebrae. Many nerve ganglia are present among their fibers. Figs. 2 and 6 show early smooth muscle fibers entering the parenchymatous uterosacral ligament (6 months' fetus).

b. *Rectal fibers:* (Figs. 2 and 7). These fibers sweep downwards and medially from the posterolateral aspect of the cervix and passing about the upper posterolateral wall of the vagina, swing into the rectum in its anteromedial area, where they are lost in its circular and longitudinal coats.

c. *Posterior vaginal fornix fibers:* (Fig. 8). From the posterolateral aspect of the cervix slightly below the internal os, short fibers pass to the musculature of the posterior vaginal fornix.

d. *Rectovaginal septum fibers:* (Figs. 2 and 7). Fibers sweep in from the recto-vaginal junction, passing between the posterior vaginal wall and anterior rectal wall, where they decussate and are lost on the walls of these structures.

Besides these distinctive strands enumerated above, short fibers enter the anterior and posterior peritoneal layers of the broad ligament, from the corresponding uterine surfaces, and end deep in the endothelium.

#### DISCUSSION

During the last three months of fetal life, smooth muscle tissue exists in definite masses in the subperitoneal pelvic space. The arrangement of the tissue is identical with that in the adult, except that it is much less massive and the direction of the bands varies owing to the difference between the positions of the pelvic organs in fetal and adult life. The smooth muscle tissue is not confined only to the areas immediately surrounding blood vessels and nerves. Most of it is made up of strands entirely independent of these structures. When they are reconstructed and viewed from the superior aspect, the direction of the fibers leads one to consider the tissue as an imperfect "diaphragm" of smooth muscle converging on the uterine cervix. It is true that there are other parts of the tissue which do not enter into the formation of this "diaphragm" but are seen as independent masses of muscle tissue, or as continuations upward of the lateral ligaments (of Mackenrodt) on to the lateral edges of the uterus. The round ligament is, of course, entirely independent. The observations recorded above raise some interesting problems: (a) The origin of the muscle cells; (b) the function of the muscle tissue in the adult.

The first problem cannot be solved from the material at my disposal. In a six months' fetus, e.g. (Fig. 6), it has been possible to make out masses of undifferentiated cells lying in areas corresponding closely to those in which smooth muscle tissue becomes apparent at a later date. These cells are in all probability primitive myoblasts, but it is not possible to be certain whether they are migrating cells from the smooth muscle walls of the Müllerian ducts, or are spe-

cializations in situ of the mesenchymatous cells within the urogenital septum. It is quite clear, however, that the tissue is not derived from the musculature of the blood vessels, as many of the anlagen of the strands are entirely separate from any vessels possessing a muscular coat. Further study is necessary to clear up this question. With regard to the function of these fibers, it is obvious that no direct evidence can be presented. Two sources of knowledge provide relevant facts: (a) the anatomic arrangement of the fibers, and (b) the surgical procedures and observations which have been undertaken to repair or reconstruct the pelvic floor in cases of prolapse and traumatism.

The distribution of the smooth muscle is interpreted diagrammatically in Figs. 2 and 5. Its arrangement, as has been pointed out above, is in the main slinglike. Considered generally, it forms an imperfect diaphragm within the connective tissue that forms the substance of the various pelvic ligaments. This smooth muscle sling is insufficient in strength to support the pelvic viscera. There is a striking similarity between the bundles of the pelvic unstriated muscles and the component muscles of the levator. The fan-shaped ligaments of Mackenrodt resemble in direction, if not in extent, the iliococcygeus and some of the pubococcygeus fibers, and the pubocervical and the cervicovesical fibers have striking counterparts in the subdivision of the pubococcygeus, which is more properly called the sphincter vaginae.

If the muscle tissue cannot be considered a diaphragm except so far as its defects are made whole by fascia, it may have other functions according to the arrangement of its several parts. Fascia, in itself, is not unusually found in regions subjected to intermittent and varying degrees of tension. Usually it is most developed where it can respond as a passive elastic agent which must be extended beyond its quantum of elasticity. Smooth or striated muscle, however, having the property of maintaining "tension" or "tonus," can withstand extension or stretching, which could not be tolerated by mere fascia. If, however, owing to nutritional or mechanical factors, its power of maintaining a high tonus is lessened, then it is a much less efficient supporting structure than is fascia. Smooth muscle has the property of maintaining, within fairly narrow limits, the same tonic force irrespective of the degree of stretch to which it is subjected until the limit of its elasticity is reached. From then on it behaves as an inactive fascial tissue. These considerations, when applied to the arrangements of the tissue as described above, are of fundamental importance. The muscle tissue is found precisely in those regions where it is necessary to permit considerable dilatation, contraction, or movement of organs, meanwhile maintaining some degree of control of the movements of these organs independently and in relation to each other.

It is obvious that it is necessary to have a mechanism to restore the normal state after a major dilatation, etc., of one or more of the organs. It is equally obvious that fascia would be ineffective in such contingencies. Viewing now the smooth muscle in terms of actual mechanism, the following principal arrangements can be recognized: (a) The mechanism for fixation of the cervix uteri; (b) the mecha-

nism of sphincteric arrangement; (c) the mechanism of special fiber units.

a. *The mechanism for fixation of the cervix uteri:* The human uterus lies in the physiologic position of antelexion and anteversion. The body of the uterus lies in the direction of the axis of the pelvic inlet, with the fundus directed upward and forward, and the cervix pointing downward and backward. Because of the strategic attachment of its fibers the extravisceral smooth musculature plays an important role in maintaining the uterus in its normal position. The three groups of fibers, anterior, lateral, and posterior, radiating from the uterus to their insertions, help to maintain the cervix at a fixed level and in the direction of the axis of the pelvis. The anterior group, when contracting, make taut the posterior group fibers; they are its tensors and antagonists; conversely, the posterior group are the antagonists of the anterior group fibers. Nevertheless, when both groups are contracting under equal tension, they unite in a synchronous effort to promote fixation. The lateral fibers in the broad ligament as a group are attached slightly anterior to the central axis of the uterus, and help to maintain the uterine body anterior to the axis of the pelvis. The upper fibers of this group being inserted into the subperitoneal connective tissue, help to hold the uterus suspended on the connective tissue scaffolding. The lower fibers because of their insertion into the arcus tendineus, unite with the upper fibers in suspending the area of the internal os at a fixed level. The posterior fibers are the auxiliaries of the round ligaments.

The round ligaments, in association with the upper portion of the broad ligaments in a coronal plane, are fixed anterior to the midline of the uterus, and thus help to maintain the antelexion and anteversion of this organ. The maintenance of antelexion and anteversion is also assisted by the downward intra-abdominal pressure. The uterus and the broad ligaments constitute the deflecting plane. The uterus is pressed against the posterosuperior surface of the bladder, which in turn rests upon the cervicopubic ligaments, thus making them tense, while at the same time tension will be more or less passed on to the lateral and posterior portions of the smooth muscle diaphragmatic sling. A uterus in malposition, such as in retroversion and retroflexion, will have this condition accentuated by the continued force of intra-abdominal pressure. The smooth muscle diaphragm in its posterior portion will have tension exerted upon it, the uterosacral ligaments will soon become elongated and their elasticity lost. The equilibrium between the anterior and posterior fiber groups will ultimately be destroyed, and the malposition will be further accentuated, and eventually will result in a descensus uteri. The fascial structures with which this smooth musculature is associated are also of importance in determining uterine position. Beneath the smooth muscle diaphragm is a stratum of connective tissue, following very much the same general outline as the smooth muscle. Its fibers converge medially to their insertion at the cervix. The tissue also forms considerable deposits of connective tissue around the pelvic viscera, especially at the vaginal fornices.

b. *The mechanism of sphincteric arrangement:* Smooth muscle fibers in the lateral pelvic gutters, in the anteroposterior plane above the vaginal fornices, and between the bladder and cervix, and cervix and rectum, have a sphincteric arrangement (Fig. 9). The boundaries of this lateral pelvic gutter are, laterally, the converging fibers of the levator ani muscle and the arcus tendineus; to the medial side lie the lateral and posterolateral borders of the base of the bladder; the vesicovaginal junction; the lateral vaginal fornix; the rectovaginal junction, and the lateral rectal wall. In this plane, smooth muscle fibers encircle the base of the bladder, the vaginal fornices, and the rectum (Fig. 9).

At the lateral vesicovaginal junction, condensations of smooth muscle exist, in whose meshes are nerve ganglia and vessels. From this vesicovaginal junction, smooth muscle fibers proceed in a circular direction about the upper anterior vaginal fornix, to meet fibers from the corresponding areas of the opposite side, i.e., decussating fibers in vesicovaginal septum (Fig. 9). At the rectovaginal junction an analogous arrangement is present, i.e., the fibers decussate in the rectovaginal septum (Fig. 7). Nerve ganglia are present in greater numbers in this area. The distribu-

tion of the fibers is such as to imply a sphincteric function. Physiologically the marked changes both in size and configuration that the pelvic viscera frequently undergo, necessitate some compensating mechanism in the surrounding tissue.

Dilatation of the connective tissue diaphragm, to the extent of permitting the passage of the fetal head, demands a great stretching of this poorly contractile tissue, which of itself could not assume its original dimensions as it contains little, if any, elastic tissue. The return to the normal post-partum state is assisted by the closely associated smooth muscle diaphragm which has the power of greater extensibility. The fibromuscular diaphragm is not necessarily injured in normal childbirth. Dilatation of the uterus and cervical canal will slacken the tautness of the fibromuscular diaphragm, while return to the normal size of this viscus will renew the tension of the musculofascial diaphragm.

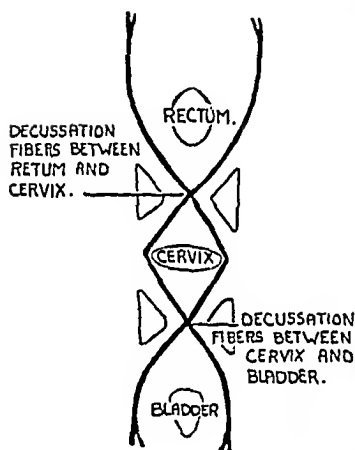


Fig. 9.

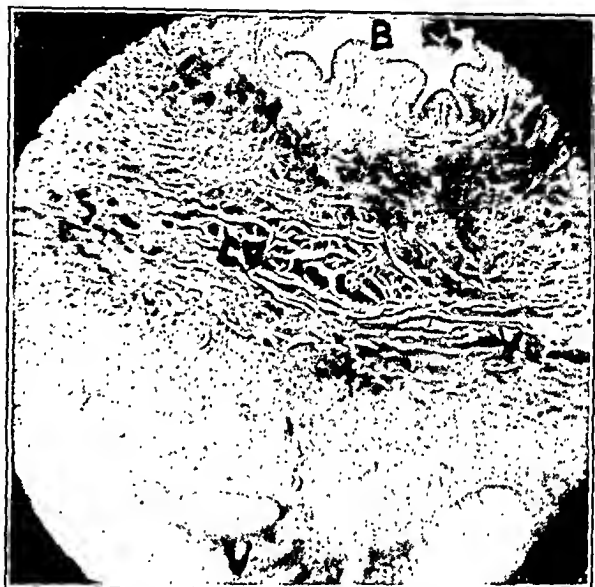


Fig. 10.

Fig. 9.—Decussation fibers.

Fig. 10.—Vesicovaginal septum. B., bladder; C.V., cervicovesical septum; V., vagina.

*c. Consideration of special fiber units:* (1) The cervicovesical fibers of the smooth muscle diaphragmatic sheet, which terminate in the trigonal muscle, may possibly be associated with the mechanism of micturition. The lower part of the vesical sphincter and the posterior urethral floor are associated with the longitudinal fibers of the muscle of the bladder trigone. The smooth muscle fibers which run forward and upward from the lateral vesicovaginal junction into the bladder musculature, terminate at the area of the trigone. It is possible that tension on these fibers will tend to pull on the trigonal muscle and help to open the vesical sphincter in its lower half. (2) The cervicopubic fibers: The bladder sits on a musculofascial platform, the upper part of the bladder wall is distensible, but the lower part is more fixed; this is the area of the trigone. The base of the bladder may make limited excursions in a cranio-caudal, or a lateral, or an anteroposterior plane. This range of movement is facilitated by the smooth muscle content in its musculofascial floor. Deficiencies in the smooth muscle cervicopubic sheet are productive of cystocele. Should this muscular sheet be deficient, the strain will be thrown immediately on the fascial supports, which cannot well sustain continued strain, and will eventually give way at the weakest point. If the attachment of the cervicopubic sheet to the os pubis yields, the bladder and urethra will slide down behind the symphysis pubis. If the deficiency occurs in the middle part, the base of the bladder protrudes through its

herniated edges. Later the fascia yields and a cystocele develops. If the sheet yields at its cervical origin, the anterior vaginal fornix prolapses, and an associated cystocele appears, its size and position depending on the area of weakening of the cervicopubic sheet.

*The Lateral Group.*—a. Upper fibers arising from the lateral uterine wall do not reach the arcus tendineus but terminate in the subperitoneal connective tissue of the broad ligament. Other fibers are inserted into its anterior and posterior folds. This latter insertion provides a resilient supporting mechanism to the peritoneal folds of the broad ligament, while the fibers terminating in the subperitoneal connective tissue help to steady the uterus, and their contraction, in conjunction with the lower fibers, would tend to pull up the uterine artery and ureter and to obliterate the lateral vaginal fornices.

b. Lower fibers: The marked condensation of the smooth muscle fibers about the transverse part of the uterine artery, in the region of the internal os, is of great interest. It seems very probable that this large artery, running through an exceptionally loose tissue, may need such support as this smooth muscle would provide to help maintain its tone. If this is so, it would be a point of great importance in regard to the frequent occurrence of excessively dilated vessels in this area.

c. Cervicovaginal fibers from the lower group help to give support to the lateral and anterior fornices.

*The Posterior Group.*—a. Uterosacral fibers: These complete the posterior elements of the smooth muscle diaphragm, and draw the cervix backward and upward toward the sacrum. They are the tensors of the vesicovaginal septum. They help support the cervix at a fixed level.

b. Cervicorectal fibers pass as fixation bands into the muscle wall of the rectum. They are possibly supportive and prevent prolapse of the mucous membrane.

c. Cervicovaginal fibers act in a similar way to those fibers in the anterior and lateral fornices.

d. Rectovaginal septal fibers: They have been considered under septal fibers in discussing the possible sphincteric control of the smooth musculature.

#### RELATION TO THE RATIONALE OF CERTAIN SURGICAL PROCEDURES

In the foregoing discussion the suggested function of the several parts of the smooth muscle tissue has been approached upon purely structural grounds. Surgery attempts to repair the results of damage to the pelvic outlet caused by childbirth. The procedures which have been devised are numerous, a sure indication that most of the operations are ineffective. An analysis of the literature of operations for the cure of rectocele, cystocele, and descensus uteri, has revealed the fact that the smooth muscle bands within the subperitoneal pelvic tissue have been consistently ignored or their existence not realized by many surgeons who have invented new methods of restoration. It is not extraordinary, therefore, that one should find that the most successful of the repair operations are those whose authors have consciously or unconsciously realized the importance of using certain "fasciae" which, in reality, are mainly smooth muscle. Basing his conclusions on anatomic data, Fothergill, in 1907, clearly established that the smooth muscle and connective tissue attached to the sides of the cervix and vagina are the important combinations which hold the bladder, uterus and vagina in position. He concluded that the disturbance of these musculofascial planes permitted a hernia of the pelvic viscera, through their weakened lines of support, and that restoration to normal lines of the disturbed planes would cure the

hernia. With this premise, he devised the operative procedure of denuding the vaginal mucosa and separating along the avascular line of cleavage between the vagina and bladder (Fig. 3) and performing "fascial lapping" of the vesicovaginal and rectovaginal septa. Later he added cervical amputation to his original operation. This "fascial lapping" reduced the operative risk very much, and obviated the necessity of abdominal section. An analysis of his operative technique shows that in his plication of the vesicovaginal and rectovaginal septa, he sutured the smooth muscle fibers of the anterior and posterior groups, under the impression that he was merely effecting reposition of the deposed lines of fascia through which the viscera had protruded. However, by this maneuver the smooth muscle planes are restored to their normal relationships, thus enabling this tissue to exert its active function in providing pelvic support.

From the date of Fothergill's epoch-making research in anatomy and surgery, numerous modifications have been added to the operative technique for the cure of prolapse. When these various modifications are examined critically, it is found that while fascial repair is often very greatly emphasized, the successful procedures can be shown to depend upon whether or not the smooth muscle groups of the fascia are utilized. Thus Fitzgibbons, in 1916, and Chipman, in 1918, both described their technique for the repair of the fascial sling. These modifications, irrespective of abdominal procedures, were differences in operative technique, rather than actual fundamental operative procedures. In the final analysis, both operators performed "fascial lapping" of the septa. They took out the slack of the vesicovaginal and rectovaginal septa by coaptation of its herniated edges, thus at the same time performing the identical maneuver in the anterior and posterior group fibers of the smooth muscle sling. Many others have added their modifications of greater or lesser degrees.

The procedure in all these operations shortens and reinforces the cervicopubic fiber groups in front; the lateral fiber group laterally; and the uterosacral group posteriorly. In the same way, other variations of operative technique have been described, and in each case those which have been proved successful make use of the smooth muscle groups. The emphasis has usually been placed merely on fascial repair, but we must now come to a realization of the fact that the essential factor in successful repair operations, as well as in the normal functioning of the supportive mechanism, is the smooth muscle content of the fascia rather than the fascia itself.

#### SUMMARY

An imperfect smooth muscle diaphragm is present and embedded in fibrous tissue, lying between the pelvic peritoneum and the superior surface of the levator ani muscle. The bands which constitute this diaphragm may be divided into anterior, lateral, and posterior groups, converging on the cervix uteri. The attachments of these to the visceral and pelvic walls, and their function, are discussed in terms

of the individual bands and the musculature as a whole. Operative procedures for the correction of sacropubic hernia are criticized, and their success or failure interpreted in the light of the dual nature of both parametrium and pelvic subperitoneal tissue.

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## CIRCULATION TIME STUDIES IN PREGNANT WOMEN WITH RHEUMATIC HEART DISEASE

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THE investigation of circulatory changes in the pregnant woman has recently been undertaken in detail by various clinics. However, similar studies in the pregnant woman with a cardiac lesion have not yet been reported.

In normal pregnancy the following observations have been made on circulation and related aspects of the circulation.

Lindhard,<sup>1</sup> Stander and Cadden,<sup>2</sup> Haupt,<sup>3</sup> Schmidt,<sup>4</sup> Schroeder,<sup>5</sup> Anthony and Hansen<sup>6</sup> have shown that the minute volume output of the heart increases, from a minimum of 15 per cent to a maximum of 74 per cent, from the fourth month of gestation onward.

Dieckmann and Wegner,<sup>7</sup> Schoenholz,<sup>8</sup> and others have shown an increase in plasma, a relative or absolute diminution in the number of formed elements, and a relative anemia.

Vital capacity remained constant or rose slightly during the course of pregnancy in the majority of patients according to Thomson and Cohen.<sup>9</sup> Alward<sup>10</sup> reported a gradual reduction of the vital capacity in the last month of pregnancy.

Gammeltoft<sup>11</sup> and Corwin, Herrick, Valentine and Wilson<sup>12</sup> showed that there was a progressive elevation of the pulse rate during pregnancy.

Greenstein and Clahr<sup>13</sup> concluded that by means of circulation studies, it is possible to demonstrate a slight but progressive retardation of blood flow in the course of pregnancy.

We have made circulation studies on a group of pregnant women with definite cardiac involvement. Our purposes were first, an endeavor to correlate the functional classification of the patient, based on subjective data, with the more objective method of circulation time; and second, to determine the value of circulation time tests in predicting the onset of cardiac failure in pregnancy.

The mortality from heart disease complicating pregnancy gathered from various clinics by Jensen<sup>14</sup> varies from 4.8 per cent to 28 per cent of all maternal deaths. The methods of lowering this mortality from cardiac failure in pregnancy are particularly effective if the condition is recognized early enough.



## PROCEDURE

Nineteen pregnant women with rheumatic heart disease were selected from the Prenatal Clinic of the Morrisania City Hospital. If any other complication existed the woman was rejected for this investigation. The patients were instructed to return to the clinic every two weeks for physical examination and determination of their functional classification according to the criteria of the New York Heart Association, and every four weeks for circulation time rates. Incomplete records were due to lack of cooperation of the patient or late registration at the clinic. If the patient was hospitalized, readings were taken more often. Every patient had at least one electrocardiogram and one fluoroscopic examination during the gestation. The history and physical examination of each patient were recorded in the special form prescribed by the American Heart Association.

There were 23 pregnancies in the group of 19 women. Two of the pregnancies were terminated at a different institution.

## METHODS

The arm-tongue time was measured according to the procedure of Fishberg, Hitzig and King.<sup>15</sup> With the patient at rest for fifteen to twenty minutes, 3 c.c. of a concentrated solution of saccharin were injected rapidly into the antecubital vein through an 18 gauge needle. The patient was instructed to announce when a sweet taste was first detected at the base of the tongue. Timing was begun from the first drop injected. This is the arm-tongue time and measures the passage of blood through the right and left sides of the heart.

With the needle in situ, the syringe was removed and replaced by one containing 3 c.c. of a 10 per cent ether solution in sterile distilled water. The patient was instructed to exhale forcefully, and the solution was injected rapidly. The time was measured by means of a stop watch from the beginning of the injection until the moment the examiner detected the odor of ether. This measures the arm-lung time<sup>16</sup> or the passage of blood through the right heart as far as the arterial capillaries of the lung.

Of the 19 cases studied, 16 women had mitral stenosis and insufficiency, one had mitral stenosis, one had mitral insufficiency, and one had mitral stenosis and insufficiency and aortic stenosis and insufficiency. Two of the patients who originally showed mitral stenosis and insufficiency developed aortic insufficiency during the subsequent pregnancies. Seven were primiparas and the remaining 12 multiparas. Twelve of these patients remained in a compensated state (Class 1 or 2a) throughout the entire pregnancy and 7 patients at some time gave symptoms or signs of cardiac insufficiency (Class 2b or 3).

*Arm-Tongue Circulation.*—There were 55 determinations of arm-tongue time done on the 19 patients. Table I demonstrates the fact that the arm-tongue time varied from month to month but did not show a constant increase or decrease as gestation progressed.

Forty-eight determinations were made when the patients did not show any signs or symptoms of cardiac insufficiency (1 or 2a). The minimum time was 7.2 seconds and the maximum time sixteen seconds (represented by black dots in Fig. 1). The normal range in nonpregnant women is eight to sixteen seconds<sup>15</sup> and in normal pregnant women from eight to 15.8 seconds.<sup>13</sup>

The remaining 7 determinations of arm-tongue time were obtained from 5 women who were in Class 2b (presented signs or symptoms of cardiac insufficiency). The circulation rates were 18, 17.4, 17.8, 20, 20, 20 and 20 seconds (represented by black circles in Fig. 1).

*Arm-Lung Circulation.*—Arm-lung circulation was determined 51 times on 18 patients (Table I). Here again as in the arm-tongue circulation there were variations in the times without any definite tendency to an increase or decrease as gestation progressed.

Forty-six of the arm-lung determinations were made when the women were completely compensated (Class 1 or 2a). These figures are represented by black dots in Fig. 2. The minimum time was 2.8 seconds and the maximum time 7.1 seconds.

Six arm-lung determinations were obtained when the women had cardiac insufficiency (Class 2b). The figures for this group were 4.6, 6.1, 6.2, 6.8, 7.0, and 7.4 seconds (represented by black circles in Fig. 2).

The arm-lung time in normal nonpregnant women is four to eight seconds<sup>15</sup> and in normal pregnant women 2.5 to 7 seconds.<sup>12</sup>

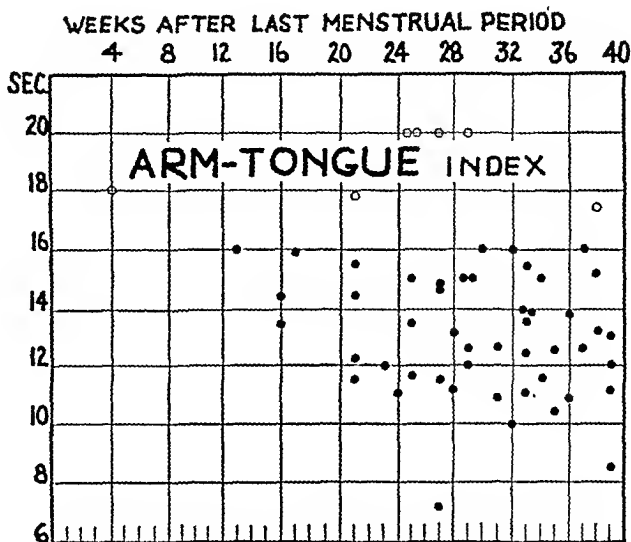


Fig. 1.

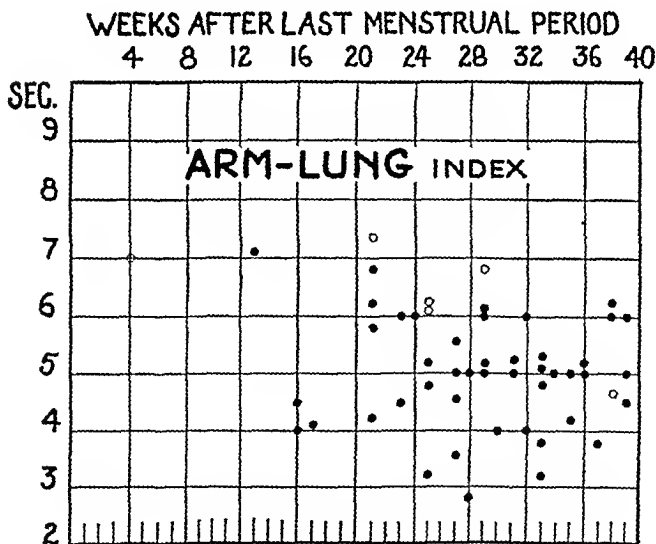


Fig. 2.

#### DISCUSSION

Blumgart<sup>17</sup> showed that the greatest part of the time required for the blood to pass from the antecubital vein through the right and left sides of the heart is consumed in the lung capillaries, the other components being negligible factors. In other words, circulation time really measures the time required for the passage of blood through

TABLE I

CASE	AGE	PARITY	PERIOD OF GESTATION (WEEKS)	CARDIAC DIAGNOSIS				PULSE RATE	BLOOD PRES.	CIRCULATION TIME		HISTORY OF DECOMPENSATION	REMARKS
				ETIOLOGIC	ANATOMIC	PHYSIOLOGIC	FUNCTIONAL CAPACITY			ARM-LUNG (SEC.)	ARM-TONGUE (SEC.)		
1	35	5	33 37	Rh. Fev.	MI* MS EH	RSR†	2a 2a	112 104	125/ 70 140/ 80		15.4 16.0	No	Spontaneous delivery
2	28	2	13 17 21 25 29 34 38	Rh. Fev.	MI MS EH	RSR	2a 2a 2a 2a 2a 2a 2a	100 90 102 100 88 96 104	120/ 90 125/ 70 130/ 80 110/ 70 115/ 70 120/ 80 130/ 90	7.1 4.1 4.2 3.2 6.1 6.2	16.0 15.9 11.4 13.4 15.0 15.2	No	Spontaneous delivery an- encephalic monster
3	22	0	25	?	MI MS EH	Tachy- cardia	2b	132	130/ 90	6.1	20.0	No	Spontaneous premature delivery, 27th week. De- compensation 2 days ante partum
4	26	4	39	?	MI MS EH	RSR	1	104	118/ 90	6.0	11.1	No	Spontaneous delivery
5	20	0	23 27 31 35	Rh. Fev.	MI MS EH	RSR	2a 1 1 1	96 100 100 104	120/ 70 135/ 70 115/ 80 110/ 80	6.0 4.6 5.3 5.0	7.2 12.6 12.5	No	Low forceps

6	29	1	21 25 29 33 38 39	Rh. Fev.	MI MS EH	RSR	2a 2a 1 2a 2b 2a	112 92 84 92 76 78	90/ 60 85/ 50 80/ 50 80/ 50 100/ 70	5.8 5.2 5.0 5.1 4.6 13.0	15.5 11.6 12.6 12.4 17.4 13.0	No	Spontaneous delivery. Upper resp. infection in 38th wk.
7	28 31	5 6	16 4	Rh. Fev.	MI MS EH EH	RSR RSR	2a 2b	80 96	120/ 70 120/ 80	4.5 7.0	13.4 18.0	No No	Spontaneous delivery Vaginal hysterotomy and sterilization
8	25	0	16 25 27 29 30 32	Rh.	MS EH	RSR	2a 2a 1 2a 2a 2a	84 76 85 84 100 96	120/ 65 110/ 60 110/ 60 110/ 70 110/ 60 95/ 50	4.0 4.8 3.6 6.0 4.0 6.0	14.4 14.6 15.0 16.0 16.0	No	Decompensation, 29th week. Premature del. 8th mo. Car. failure post partum
9	24	1	21 27 31 35	Rh. Fev.	MI MS EH	RSR	2a 2a 2a	92 120 120 104	110/ 75 110/ 60 110/ 60 120/ 60	6.8 5.6 5.0 4.2	12.2 11.4 10.8 10.4	No	Spontaneous delivery
10	33	0	21 25 27 29	?	MI MS EH	RSR	2a 2b 2b 2b	96 90 100 92	120/ 80 100/ 60 100/ 65 100/ 70	6.2 6.2 6.8	14.4 20.0 20.0 20.0	No	Premature delivery 8th mo. Decompensation in labor
11	28	0	21 25	Rh. Fev.	MI MS EH	RSR	2b 2a	120 88	120/ 70	7.4	17.8 15.0	No	Decompensation 5th mo. Induction of labor 6th mo.
12	19	2	32 36	?	MI EH	RSR	2a 2a	88 104	118/ 62 125/ 60	4.0 5.0	10.0 10.8	No	Spontaneous delivery

\*MI, Mitral insufficiency; MS, mitral stenosis; EH, enlarged heart; AI, aortic insufficiency; AS, aortic stenosis.

†RSR, Regular sinus rhythm.

TABLE I—CONT'D

CASE	AGE	PARITY	PERIOD OF GESTATION (WEEKS)	CARDIAC DIAGNOSIS				PULSE RATE	BLOOD PRES.	CIRCULATION TIME		HISTORY OF DECOM-PEN-SATION	REMARKS
				ETIOLOGIC	ANATOMIC	PHYSIO-LOGIC	FUNC-TIONAL CAPACITY			ARM-LUNG (SEC.)	ARM-TONGUE (SEC.)		
13	22	2	36	Rh. Fev.	MI MS EH	RSR	2a	72	105/ 65	5.2	13.8	No	Spontaneous delivery
14	18	0	38	Rh. Fev.	MI MS EH	RSR	1	84	130/ 70	6.0	13.2	No	Low forceps
15	32	1	24 28 33	Rh. Fev.	MI MS AI AS EH	Tachy-cardia	2a 2a 2a	132 90 80	130/ 42 144/ 40 145/ 20	6.0 2.8 4.8	11.0 11.1 14.0	No	Class 2b in 5th mo. De-compensation in labor
16	22	1	34 39	?	MI MS EH	RSR	2a 2a	116 100	142/ 90 135/ 80	5.0 5.0	11.5 8.5	No	Spontaneous delivery
17	27	4	27	Rh. Fev.	MI MS EH	RSR	2a	108	110/ 60	5.0	14.8	No	Spontaneous delivery
18	22 24	0 1	39 23 29 33 37	Rh. Fev.	MI MS EH MI MS AI EH	RSR RSR	2a 2a 2a 1 2a	80 84 88 80 100	140/100 135/ 75 120/ 60 128/ 65 130/ 60	4.5 4.5 5.2 3.4 3.8	12.0 12.0 12.0 11.0 12.6	No     No	Low forceps Spontaneous delivery
19	27 29	1 2	33 28 33	Rh. Fev.	MI MS EH MI MS AI EH	RSR RSR	1 2a 2a	92 120 100	120/ 60 138/ 70 135/ 60	3.8 5.0 5.4	13.8 13.1 13.5	No     No	Spontaneous delivery Spontaneous delivery

the lungs, and increase or decrease in time reflects a corresponding alteration in the speed of pulmonary circulation.

In rheumatic heart disease with mitral involvement, failure of the circulation is ushered in by a relative weakening and insufficiency of the left side of the heart. This results in a damming back of blood flowing through the pulmonary bed. Since arm-tongue time is almost wholly a measure of the rate of blood flow through the pulmonary bed, a retardation of flow will give a prolonged arm-tongue time (Blumgart<sup>17</sup>).

The value of circulation time determinations is demonstrated in the following cases. Cases 3 and 10 had arm-tongue circulation rates well above the maximum for normal. In spite of the prolongation of arm-tongue times the women denied symptoms of cardiac insufficiency. They subsequently developed marked cardiac failure. These observations indicate the interrelation between circulation time and cardiac insufficiency, and demonstrate the advantage of an objective method for the determination of circulatory insufficiency in contrast with the relatively inaccurate history obtained from some of the patients.

Arm-tongue circulation rate was used once to rule out cardiac decompensation in a patient who was very desirous of an abortion. This woman was a para iv gravida v who entered the hospital in her second month of gestation with a history of having had two therapeutic abortions at two different hospitals and being unable to do any housework at all because of severe dyspnea. The woman was very obese, weighed 244 pounds and was 60 inches tall. Physical examination did not reveal any findings of heart disease or cardiac failure. The arm-tongue circulation rate was 12.8 seconds and the arm-lung time 3.8 seconds (within normal limits). Replies to our inquiries from the two hospitals did not corroborate her statements. This further emphasized our diagnosis of malingerer. The patient was discharged without interrupting the gestation.

At no time did we encounter any prolongation of the arm-lung circulation rate. Evidently there was no failure of the right side of the heart in any of the cases in this series. Even among those women with increased arm-tongue times the arm-lung times were within normal figures.

Case 8 illustrated an extremely interesting manifestation of apparent left heart failure induced by an overactive right heart during the twenty-ninth week of gestation. The patient had been well compensated all along until she undertook a walk of approximately three miles at a fast pace. She suddenly became dyspneic and cyanotic, and began to cough up frothy fluid. She was immediately hospitalized and given  $\frac{1}{4}$  gr. of morphine sulphate,  $\frac{1}{75}$  gr. of atropine sulphate and 50 c.c. of 50 per cent glucose intravenously. Within two hours her condition had improved so considerably that she was well able to leave the hospital in good condition by the third day after admission.

McGinn and White<sup>18</sup> have described a series of six cases where pulmonary edema developed in the presence of uncomplicated mitral

stenosis. It was their contention that there is a considerable difference in prognosis between those cases where the left ventricle is still efficient and those cases of pulmonary edema where there is enlargement and failure of the left ventricle. The pulmonary edema which develops in cases with an intact left ventricle is induced by effort, excitement or paroxysmal tachycardia. The strong right ventricle of these hearts expels more blood into the pulmonary circuit than can be passed through the stenosed mitral valve. Such patients may show only cardiac asthma and in extreme instances pulmonary edema. Pulmonary edema appears at an earlier age and has a better prognosis in uncomplicated mitral stenosis than in those patients with enlargement and failure of the left ventricle.

It is also interesting to note that this patient was delivered at another hospital and went into pulmonary edema immediately after delivery. Again, she responded favorably to therapy within several hours. It would seem likely that the same mechanism which produced pulmonary edema during the twenty-ninth week of pregnancy was also responsible for her acute failure following labor. A fact which corroborates this conception is that between her attacks of pulmonary edema she was perfectly compensated, the arm-tongue and arm-lung times being within normal figures.

In attempting to show the value of circulation time studies to prognosticate the onset of cardiac failure, we found the method not always feasible. For example, Cases 15 and 8 had normal circulation times throughout pregnancy although both women went into cardiac failure, one during labor and the other immediately post partum. The cause of the cardiac failure in Case 8, immediately post partum, was the same as the cause of the attack of pulmonary edema she suffered during her twenty-ninth week of pregnancy. In Case 15, the normal circulation time figures were due to the fact that the patient was on prolonged bed rest of five months, during which time her weakened myocardium was adequate. However, the increased strain of labor producing cardiac failure indicated the true state of affairs.

It has long been known even in nonpregnant cardiacs that patients who are well compensated may develop a mild degree of decompensation with the onset of an upper respiratory infection. The occurrence of an upper respiratory infection during the thirty-eighth week of pregnancy in Case 6 was responsible for the abnormal prolongation of the arm-tongue time (17.4 seconds). The patient complained of increased dyspnea at that time. The following week the respiratory infection cleared, the arm-tongue time dropped to thirteen seconds and the patient was improved subjectively.

#### CONCLUSIONS

1. The arm-tongue circulation rate in pregnant women with well-compensated rheumatic heart disease is within normal limits.
2. The arm-tongue circulation rate in pregnant women with cardiac insufficiency is prolonged.

3. The arm-lung circulation rate in pregnant women with well-compensated rheumatic heart disease is within normal limits.

4. The arm-lung time in cardiac insufficiency (Class 2b) remains within normal limits.

5. Increase of the arm-tongue circulation rate above normal despite a denial of symptoms of cardiac weakness is an indication of present circulatory insufficiency.

6. The use of arm-tongue circulation time tests was valuable as an objective method of eliminating a patient who was desirous of an induced abortion on the basis of assumed cardiac failure.

We are indebted to Dr. Harry Aranow, Director of Obstetrics, and Dr. Edward Flood, Director of Medicine, Morrisania City Hospital, for their encouragement and advice.

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15 CLARKE PLACE  
1147 HOE AVENUE  
1075 GRAND CONCOURSE

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**Tyler, G. T., Jr.**: Endometrioma of the Umbilicus Following Caesarean Section, South. M. J. 31: 987, 1938.

The indication for cesarean section in a 26-year-old woman was an obstructed pelvic outlet caused by a displacement of one of the pubic rami following a fracture of the pelvis, sustained several years previously.

Three years after the operation the patient complained of a bloody discharge from the umbilicus which appeared at the time of her menses. There was a reddish swelling of the umbilicus. The clinical diagnosis of umbilical endometrioma was confirmed by biopsy. Thorough abdominal and pelvic examination revealed no other palpable evidence of ectopic endometrial tissue. The uterus was small and in retroposition.

Apparently the umbilical lesion developed as a direct transplant at the time of abdominal delivery. The suggestion is made that when midline incisions are employed in cesarean section, bayonet-like extension should be made to avoid the umbilicus. Other precautions against transplants of endometrial tissue consist in protecting the wound edges and abdominal cavity by gauze packs, and saline irrigation of the field following peritoneal closure in order to remove mechanically remnants of blood or uterine tissue.

ARNOLD GOLDBERGER



# CLASSIFICATION AND TREATMENT OF THE ANEMIAS OF PREGNANCY

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**A**NEMIA is a frequent complication occurring in the course of pregnancy. Realizing the importance of this, a study was conducted on the Obstetrical Service of Bellevue Hospital during the period extending from October, 1937, to July, 1938.

During this interval 881 pregnant women were studied according to the method to be described later. Four hundred twenty-five, or 48 per cent, of these women were found to have anemia on admission to the hospital during labor. The incidence of anemia rose to 72 per cent in the group receiving no active iron therapy during the ante-partum period.

## METHOD OF STUDY

A red blood count and hemoglobin determination were done, by a technician employed for this study, on every patient admitted to the prenatal clinic of Bellevue Hospital. The Sahli hemoglobinometer was used in determining the level of the hemoglobin, 14.5 gm. per 100 c.c. of blood being considered as 100 per cent. The red blood count and hemoglobin were rechecked by the same technician between the seventh and eighth months of gestation. If the red blood count was found to be below 4 million or the hemoglobin below 80 per cent, that patient was considered to have anemia. Five grains of ferrous sulfate\* was prescribed three times daily for every patient developing anemia in the ante-partum period. This therapy was continued until the end of pregnancy or until symptoms of intolerance to the iron, such as nausea, vomiting, diarrhea, or heartburn developed.

On admission to the hospital during labor, a red blood count, hemoglobin determination and hematocrit were done by a fourth-year medical student. The red count, hemoglobin and hematocrit were repeated on the eighteenth day post partum by our technician. Some of the patients showing anemia on admission to the hospital in labor were given iron therapy during the post-partum period. Others, however, were used as a control group and no iron was prescribed.

Forty-two patients were detained in the hospital during their prenatal period for intervals varying from one week to three months, during which time red blood counts, hemoglobin determinations, hematocrit and plasma protein studies were done three times weekly, by the same technician. In this group the same determinations were repeated every other day during the first ten days post partum. In 48 patients gastric analyses were done ante partum and repeated on the eighth day post partum.

The hematocrit was done with the Wintrobe tube using the technique described by Wintrobe. Six milligrams of ammonium oxalate and 4 mg. of potassium oxalate per 5 c.c. of blood were used as anticoagulant. Using this solution, the volume of the erythrocyte remained unaltered.

\*Ferrous sulfate used in the treatment of these patients was given in the form of "hematinic plastules," plain.

## CLASSIFICATION OF THE ANEMIAS

The classification presented here is one derived from the study of the hematocrit on 99 patients. It depends entirely on the size of the red blood cell and the amount of hemoglobin contained in the cell. Details of this phase of the subject will be discussed later in a separate paper.

## Classification of the Anemias of Pregnancy:

I. Macrocytic	62 per cent	III. Microcytic	2 per cent
a. Simple	47 per cent	a. Simple	1 per cent
b. Hypochromic	9 per cent	b. Hypochromic	1 per cent
c. Hyperchromic	6 per cent		
II. Normocytic	37 per cent		
a. Simple	13 per cent		
b. Hypochromic	23 per cent		
c. Hyperchromic	1 per cent		

It is interesting to note that macrocytosis occurred in 62 per cent of the anemias of pregnancy encountered during this study. Dieckmann and Wegner also found that in the period of gestation from ten to thirty-five weeks the erythrocytes differ from the average normal in that they are a little larger and contain more hemoglobin.

In 47 per cent of the group showing macrocytosis the mean corpuscular hemoglobin remained normal or very slightly reduced. The mean corpuscular hemoglobin concentration, however, was below normal because the increase in size of the red blood cell was not associated with a corresponding increase in hemoglobin. In 9 per cent there was a moderate to marked decrease in both mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration, resulting in hypochromia. In 6 per cent the size of the red cell and the amount of hemoglobin were both increased. It appears from this study that the milder forms of the macrocytic hyperchromic anemias of pregnancy may be diagnosed more readily if hematocrit determinations are done.

In 37 per cent the size of the red blood cell remained within normal limits. Here again the hemoglobin content of the cell was normal, reduced or increased in amount.

Microcytosis was found to occur in only 2 per cent. One of these was associated with marked hypochromia.

## TREATMENT

Analysis of the effect of iron on the anemias of pregnancy: 881 pregnant women are included in this study; 325 received iron in the form of ferrous sulfate, 5 gr. three times daily, one-half hour after meals, during the prenatal period. The average duration of iron therapy was 53.31 days. Five hundred and fifty-six received no iron. Patients receiving iron less than ten days were included in this non-treated group.

Four hundred and twenty-five, or 48 per cent, of all patients admitted to the hospital during labor had an anemia. Of the 325 patients receiving iron ante partum, 28 per cent were found to have a mild anemia on admission to the obstetric service during labor. However, of the total number of 307 pregnant women receiving no iron therapy prenatally, 72 per cent were found to have an anemia. Four hundred and fifty-six patients had normal readings of the red blood count and hemoglobin at the time of admission during labor and 55 per cent of this group had received no iron during the prenatal period.

Table I shows the results of treatment with iron during the prenatal period in 325 pregnant women who had anemia. Group A represents 118 parturient women who received iron prenatally, but who continued to show a mild anemia on admission during labor. The average red blood count during the prenatal period, before the start of iron therapy, in this group was 3.65 M and the average hemoglobin was 65.82 per cent (9.54 gm.). On admission during labor the average red blood count rose to 3.88 M and the average hemoglobin to 77 per cent (11.17 gm.), an increase of 0.25 million in red blood cells per c. mm. and 1.63 gm. in hemoglobin per 100 c.c. of blood.

Group B consists of 207 women who had an anemia during the prenatal period and who received iron. At the start of iron therapy the average red blood count was 3.73 M and the average hemoglobin 66 per cent (9.56 gm.). On admission to the hospital during labor, the red blood count and hemoglobin were at normal levels, the average red blood count being 4.31 million per c. mm. and the average hemoglobin 83.1 per cent (12.05 gm.). This represents an increase of 0.58 million red blood cells per c. mm. and 2.49 gm. of hemoglobin per 100 c.c. of blood.

TABLE I.—RESULT OF THERAPY WITH IRON DURING THE PRENATAL PERIOD OF 325 PATIENTS HAVING SECONDARY ANEMIA OF PREGNANCY

GROUP	NUMBER	DAYS OF IRON THERAPY	AT START OF THERAPY DURING PRENATAL PERIOD			DURING LABOR		
			R.B.C.—MILLIONS PER C. MM.	HGB		R.B.C.—MILLIONS PER C. MM.	HGB	
				%	GM.		%	GM.
A	118	46.62	3.63	65.82	9.54	3.88	77.0	11.17
B	207	60.00	3.73	66.08	9.58	4.31	83.1	12.05
Average	325	53.31	3.68	65.95	9.56	4.09	80.05	11.61

TABLE II.—RED BLOOD COUNT AND HEMOGLOBIN CURVE ON 307 PREGNANT WOMEN RECEIVING NO IRON DURING THE PRENATAL PERIOD

NUMBER	PRENATAL PERIOD			DURING LABOR		
	R.B.C.—MILLIONS PER C. MM.	HGB		R.B.C.—MILLIONS PER C. MM.	HGB	
		%	GM.		%	GM.
152	3.06	47.6	6.90			
307				3.01	56.25	8.16

For the entire group of 325 parturient women who received iron ante partum, the average red blood count was found to rise from 3.68 M at the onset of iron therapy to 4.09 M on admission during labor. Similarly the average hemoglobin rose from 65.95 per cent (9.56 gm.) to 80.05 per cent (11.61 gm.). This suggests that 1 gm. of ferrous sulfate given daily during the prenatal period to patients developing anemia will produce a definite rise of the red blood count and hemoglobin.

In contrast, Table II represents the average blood picture seen in 307 pregnant women who received no iron during the prenatal period; 152 of these women who were seen ante partum were found to have an average red blood count of 3.06 M and an average hemoglobin of 47.6 per cent (6.90 gm.). In comparing these red blood count and hemoglobin readings taken during comparable prenatal periods, it is seen that the severity of the anemia in the nontreated group is greater than either of the Group A or B who received iron prenatally (Figs. 1 to 3). This suggests that iron therapy will not only cause an increase in the red blood count and hemoglobin but even if completely normal levels are not reached, a further decrease in the levels of the red blood count and hemoglobin is prevented.

The level of the red blood count and hemoglobin during labor in this nontreated group is seen to be strikingly lower than in the group receiving iron (Figs. 2 to 4). The average red blood count per c. mm. was found to be 3.01 M. and the average hemoglobin was 56.25 per cent (8.16 gm.).

Among the 325 women who received iron ante partum, only 61 patients had a normal red blood count before the start of iron therapy, but on admission to the hospital in labor, 234 were found to have a normal red blood count (Figs. 1 and 2). Similarly 224 had normal levels of hemoglobin during labor contrasted to 4 during the prenatal period before the onset of iron treatment (Figs. 3 and 4).

Only 27 of the 307 patients who received no iron in the ante-partum period had a normal red blood count (Fig. 2), and only 67 were found to have normal hemoglobin determinations during labor (Fig. 4). In contrast, among the group of 325

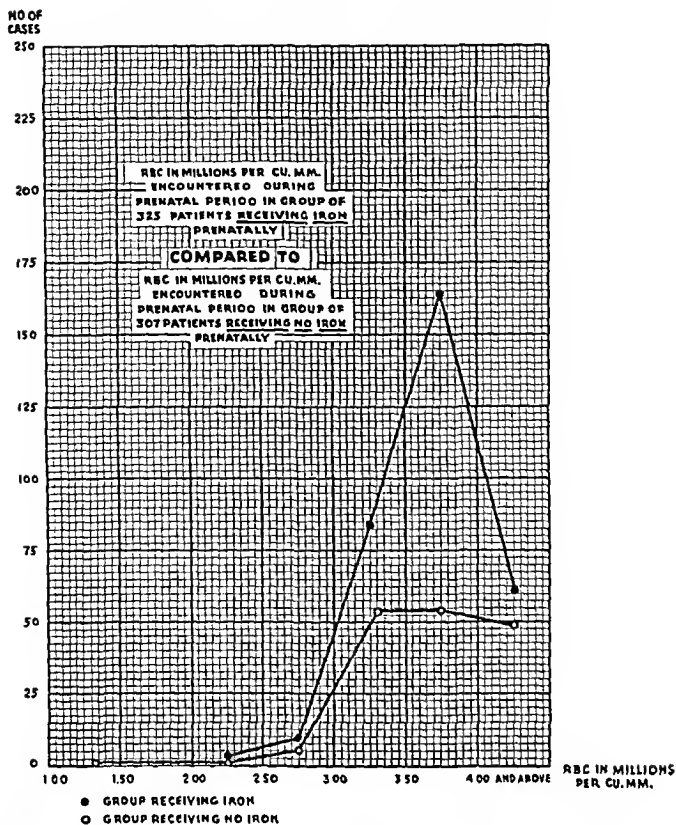


Fig. 1.

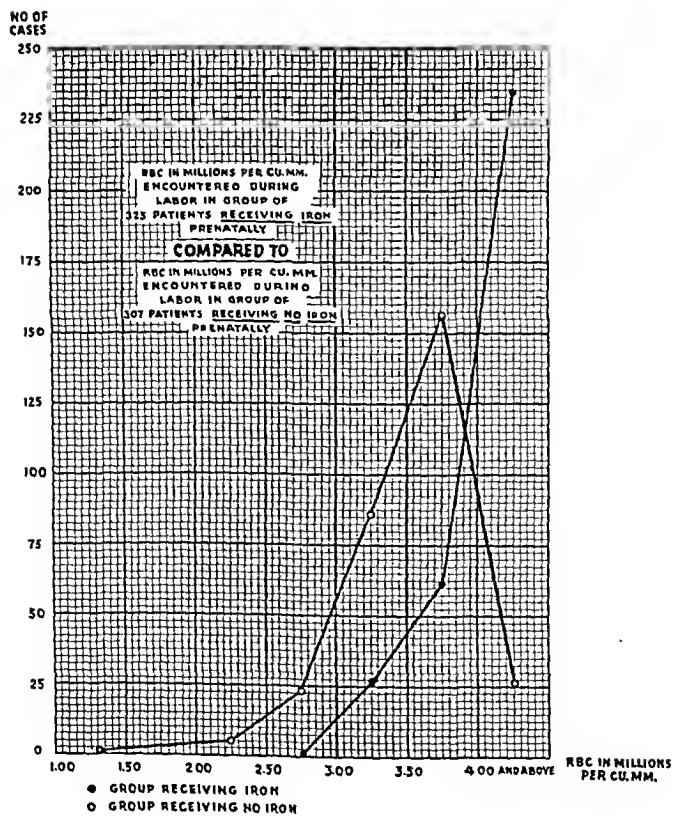


Fig. 2.

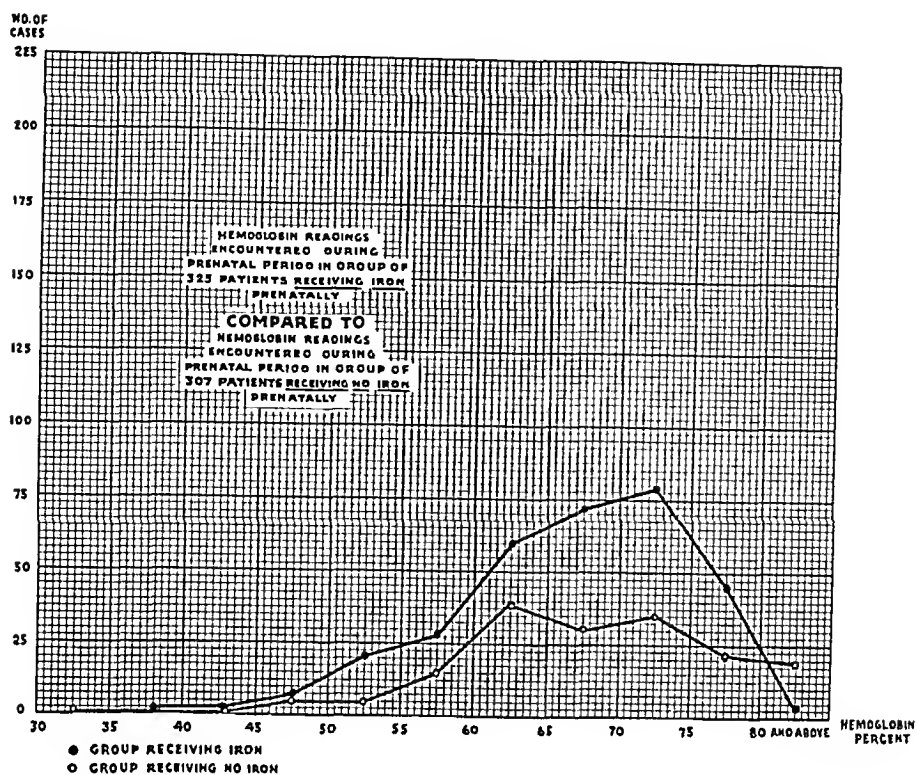


Fig. 3.

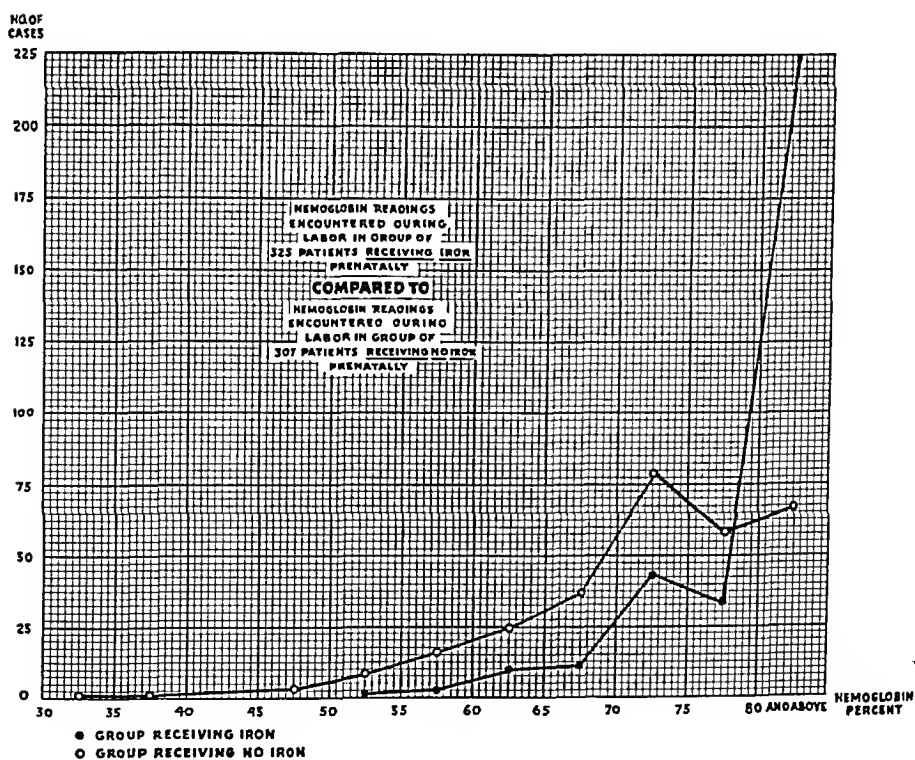


Fig. 4.

women receiving iron prenatally, 234 had normal red blood cell levels and 224 had normal hemoglobin readings on admission to the hospital while in labor (Figs. 2 and 4). Only 1 patient among this treated group had a red blood count below 3.00 million during labor, whereas 29 had counts below this figure in the group receiving no iron ante partum (Fig. 2). There were 3 patients among the treated group who had hemoglobin readings below 60 per cent compared to 29 in the nontreated group (Fig. 4). Further scrutiny of Figs. 1 to 4 shows clearly the lower levels in red blood count and hemoglobin in the group of patients who did not receive the benefit of iron prenatally. The hemoglobin levels reached as low as 30 per cent and the red blood count as low as 1.35 per cent in the nontreated group.

#### ROLE OF DIET IN THE TREATMENT OF THE ANEMIAS OF PREGNANCY

It is extremely difficult to control the diets in the group of patients who attend the prenatal clinic in Bellevue Hospital. Therefore each patient was questioned closely about her diet, an attempt being made to determine the proportion of meat, fresh vegetables, fruits, milk, and eggs in the daily dietary. Based on this questionnaire the diets were labeled as adequate, fair, or inadequate. Patients eating red meat, eggs, fresh fruits and vegetables, and one quart of milk daily were considered to have an adequate diet. Patients eating meat and eggs several times weekly, fresh fruits and vegetables daily, and 1 quart of milk daily were considered as having a fair diet. Patients eating foods low in protein and in iron content were considered as having inadequate diets.

The cases were further subdivided into noncomplicated and those complicated by diabetes, syphilis, pre-eclampsia, pyelitis, cardiac disease, etc.

A table was constructed to show the value of an adequate diet in aiding in the control of the anemias of pregnancy. The noncomplicated cases receiving iron during the prenatal period were found to be little affected by diet. Iron therapy produced an increase in the levels of the red blood cells and hemoglobin regardless of whether or not the patient was partaking of an adequate, fair, or inadequate diet. Iron which was given during the prenatal period apparently was sufficient to compensate for the lack of sufficient amounts of iron in the dietary. However, cases which were complicated by one of the frequent prenatal complications such as pre-eclampsia, pyelitis, etc., required the addition of an adequate diet rich in iron and protein. This group of patients having some form of prenatal complication and receiving only a fair or inadequate diet tended to show a persistence of the anemia in spite of iron therapy.

The effect of an adequate diet was more noticeable in the group of patients who received no iron prenatally. The average red blood count and hemoglobin were found to decrease slightly as the diet became less satisfactory. Thus in the group receiving an adequate diet the average red blood count per c. mm. was 3.69 million and the average hemoglobin 71.18 per cent; in the group receiving a fair diet the average red blood count was 3.57 million and the average hemoglobin 70 per cent; in the group partaking of an inadequate diet the average red blood count was 3.52 million and the average hemoglobin 68 per cent. The drop in the average red blood count and hemoglobin was more apparent in the group of patients who had some prenatal complication such as pre-eclampsia, pyelitis, or syphilis. In this group, the patients receiving an inadequate diet had an average red blood count of 3.08 million and an average hemoglobin of 59 per cent. The patients receiving an adequate diet, however, had an average red blood count of 3.67 million and an average hemoglobin of 69 per cent.

## VALUE OF IRON IN THE POST-PARTUM PERIOD

The group of patients who received iron during the prenatal period appeared to withstand the effects of labor better than the group who did not receive iron and who subsequently entered in labor with an anemia. This statement is made on the basis of comparison of the morbidity and length of hospitalization, post partum. Morbidity was determined on the 100°, 100.4° and 101° F. standards. There were 14.8 per cent of the patients who were prepared prenatally with iron therapy who ran a morbid course post partum. The nontreated group that entered in labor with an anemia had a 19.5 per cent morbidity. Similarly the length of hospitalization post partum was greater in the nontreated group. The average number of hospital days was 10.35 in the group of patients receiving iron during the ante-partum period, and 11.05 in the group receiving no iron.

The patients in Bellevue Hospital are kept ten days post partum, and then discharged. The period is too short to determine any significant immediate effects of iron given during this short post-partum period. Immediately following delivery, some patients having an anemia, i.e., a red blood count of less than 4 million per c. mm., or a hemoglobin less than 80 per cent, were given 5 gr. of ferrous sulfate three times daily, while others, used as a control group, were not given iron. The red blood count and hemoglobin determination were repeated on the eighth day post partum. Little significant difference could be noted during this short period between the group receiving iron and the group receiving no iron post partum.

There was a slight rise in the red blood cells per cubic millimeter and in the hemoglobin on the eighth post-partum day in both the treated and nontreated groups. However, the group receiving iron post partum had an average red blood count per c. mm., 0.01 million higher and an average hemoglobin 4 per cent (0.58 gm.) higher than the group receiving no iron.

One gram of ferrous sulfate daily was given to approximately half of the post-partum patients with anemia for a four-weeks period following discharge from the hospital. At the end of this time the patients receiving iron showed slightly higher levels of the red blood cells and hemoglobin than those patients who were not given the benefit of iron therapy.

## DISCUSSION

Iron is of decided value in the treatment of anemia developing during pregnancy. Ferrous sulfate, 5 gr. three times daily, given one-half hour after meals, is the minimum dose to be used.

A small percentage of patients, however, will not respond with a complete return to normal of the red blood count or hemoglobin during the prenatal period. A mild form of anemia may continue until after delivery, but by the eighth day post partum there is a tendency for spontaneous resumption of normal levels in the red blood cells, hemoglobin and the hematocrit. Whether this lowered level of the red blood count and hemoglobin in the latter part of pregnancy is entirely physiologic and due to hydremia is difficult to determine. Studies in plasma proteins which were done would lead one to believe that the rise in the red blood count and hemoglobin after delivery is due partially to concentration of the blood resulting from the loss of fluids.

Bethell found that with the hematocrit value as a basis for calculation and on the assumption that there occurs no compensatory output of red blood cells, the lowest red blood count that may be explained solely by hydremia is approximately 3.7 M, the lowest hemoglobin is about 70 per cent. Dieckmann and Wegner and others believe that a 10 to 20 per cent lowering of hemoglobin during pregnancy may be the result of hydremia and may not represent true anemia.

These patients who appeared to be resistant to the effects of iron were given 30 gr. of ferrous sulfate daily and a high calorie diet with liver daily. After seven- to ten-days trial with this form of therapy, 3 c.c. of concentrated liver extract (10 units) was given intramuscularly daily for five days and then 3 times weekly for twenty-one days. Vitamin B<sub>1</sub> was given intramuscularly daily. If the gastric analysis showed low levels or absence of free hydrochloric acid, dilute hydrochloric acid was given by mouth. In spite of this intensive treatment a mild form of anemia persisted. Bethell also noted many instances in which the administration of iron failed either to correct or prevent anemia. These cases were found frequently to possess red blood cells of relatively large volume. However, these subjects when placed on a suitable diet (65 gm. of protein with 1 quart milk added) developed correction of the anemia with restoration of the erythrocyte volume.

Maurice Strauss believes that the hypochromic anemias of pregnancy may be completely relieved by the administration of iron in suitable doses. Corrigan and Strauss state that the hypochromic anemias in pregnancy may be prevented largely by routine iron especially in the latter months and so advise the prophylactic use of iron. Evans also testifies for the value of iron in the treatment of the anemias of pregnancy. He believes that the great majority of the anemias of pregnancy are preventable by adequate doses of inorganic iron and he too advises that "all women during pregnancy should be given inorganic iron, particularly during the last trimester." Bethell reports that anemia in pregnancy due to iron depletion may be cured by supplying iron in adequate doses.

We do not subscribe to the practice of giving iron to all women during pregnancy with the hope of preventing the development of anemia. Since one-half of the women during pregnancy do not develop anemia it does not seem reasonable to give all pregnant women iron. It is sounder practice to check on the status of the red blood count and hemoglobin several times during the course of pregnancy, as we have done, and prescribe iron only when required.

The value of dilute hydrochloric acid in the treatment of the anemias of pregnancy is questionable.

Evans suggests the use of dilute hydrochloric acid, 10 drops three times daily increasing to 40 drops, particularly during the last trimester. Mettier and Minot claim that the iron does not need to be given in an acid medium, for apparently if a sufficient dose of iron is given in an alkaline medium suitable responses of the bone marrow will ensue. However, their studies do indicate that soluble iron compounds are absorbed from the gastrointestinal tract, or utilized more readily for blood formation when administered with acid rather than with alkaline meals.

#### SUMMARY AND CONCLUSIONS

1. This is a study of 881 pregnant women, 325 of whom received 5 gr. of ferrous sulfate three times daily during the prenatal period.



2. Four hundred twenty-five, or 48 per cent, of all patients in labor were found to have an anemia on admission to the hospital. Seventy-two per cent of this number of patients showing anemia had received no iron during the prenatal period.

3. Three hundred twenty-five patients who received iron therapy during the prenatal period were found to have an average red blood count of 4.09 M and an average hemoglobin of 80.05 per cent (11.61 gm.) on admission during labor.

4. Three hundred seven patients who received no iron during the prenatal period were found to have an average red blood count of 3.01 M and an average hemoglobin of 56.25 per cent (816 gm.) on admission during labor.

5. The group of patients receiving *no* iron during the prenatal period showed far lower levels in the red blood cells and in hemoglobin than the group receiving iron. In the former group the lowest red blood count was 1.35 M and the lowest hemoglobin 30 per cent.

6. Macrocytosis was found to be present in 62 per cent of the cases showing anemia. Only 7 per cent of these anemias showed hyperehromia.

7. Inorganic iron in the form of ferrous sulfate, 1 gm. daily, is effective in restoring the red blood count and hemoglobin to normal levels.

8. An adequate diet in itself will not prevent the development of anemia during pregnancy.

9. One gram of ferrous sulfate which is given during the prenatal period apparently is sufficient to compensate for the deficient amount of iron in an inadequate diet.

10. The group of anemic patients receiving iron during the prenatal period had a 14.8 per cent morbidity as compared with 19.5 per cent morbidity in the nontreated group.

11. The average number of days of hospitalization was 10.35 in the patients receiving iron prenatally and 11.05 in the patients receiving no iron ante partum.

12. Iron therapy must be continued beyond the period of hospital stay to have any significant effect on the red blood cells and hemoglobin of the post-partum anemic patient.

We wish to express our gratitude to the Bovinine Company, Chicago, Ill., for the grant provided to cover the expenses of conducting this study.

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# THE EXCRETION OF FREE AND ACETYLSULFANILAMIDE IN HUMAN BREAST MILK\*†

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IN AN earlier paper<sup>1</sup> a study was made of the excretion of sulfanilamide in the breast milk of twenty patients who had received orally a total of 2 or 4 gm. (30 or 60 gr.) of the drug in two equal, four-hourly doses. Of the 10 patients who received the 2 gm. dose, the total amount of drug excreted in the milk varied from 3.76 to 13.67 mg.; of those who received the 4 gm. dose, the variation was from 11.77 to 54.00 mg. In terms of milligrams per cubic centimeter, the variation was from 0.006 to 0.016 and from 0.019 to 0.040 mg. per c.c. With the doubled dose of drug, considerably more than a double amount of the drug was excreted in the milk.

The purpose of the present investigation was to determine whether prolonged use of sulfanilamide at therapeutic blood levels would result in an accumulation of the drug in breast milk sufficient to be detrimental to the nursing baby.

In the previous paper, the free sulfanilamide levels in the blood and milk were compared, and it was shown that although they followed the same general course, the levels in the milk were considerably higher than those in the blood. The drug continued to be excreted in the milk even after the blood levels were negligible, but the largest total amount of drug excreted in the milk was only 1.5 per cent of that ingested (Charts 1 and 2).<sup>1</sup>

It was stated that sulfanilamide was excreted in the milk as in the urine partly in the unchanged and partly in the conjugated form, but quantitative determinations for the acetyl compound were not given. Since it is known that, at least in animals, the toxicity of acetylsulfanilamide is greater than that of the free sulfanilamide,<sup>2</sup> it was felt that further information concerning the amount of drug excreted in the conjugated form might be of value. The present study, therefore, includes graphs which compare both the free and acetylsulfanilamide levels of the blood, milk, and urine.

The patients considered were normal women studied during the third to ninth post-partum days. Since it was customary for the patients to leave the hospital on the tenth day, it was impossible to continue the study for a longer period. Two to 5 gm. of the drug were administered in 6 doses daily for a period of three days. By

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this procedure it was hoped that a fairly constant blood level might be established for comparison with the milk level. The milk was collected at four-hour intervals (alternate breasts were emptied by an electric breast pump) and determinations for both free and conju-

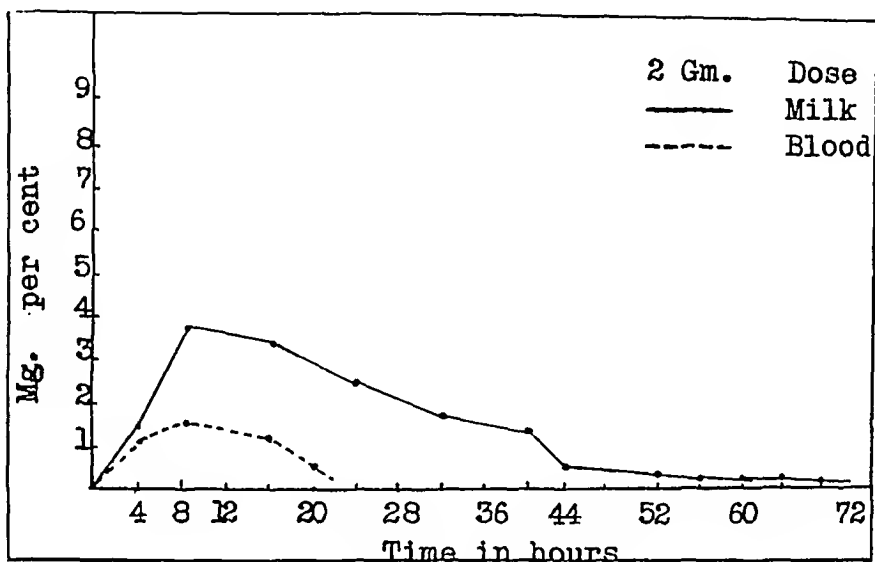


Chart 1.—Comparison of free sulfanilamide levels in the blood and milk. Dose 2 gm. (30 gr.).

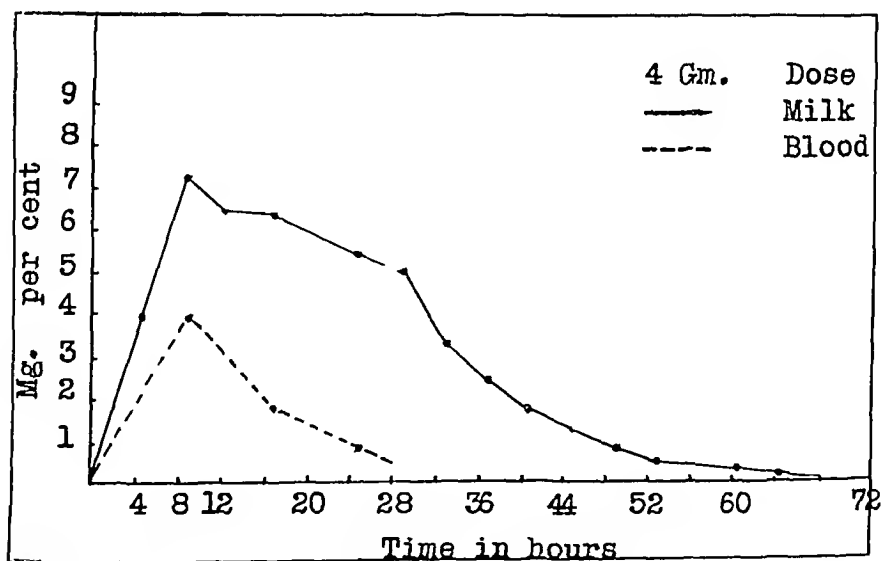


Chart 2.—Comparison of free sulfanilamide levels in the blood and milk. Dose 4 gm. (60 gr.).

gated sulfanilamide were made on each specimen. Blood was obtained twice the first day, eight and sixteen hours after medication had been begun, and at twenty-four-hour intervals thereafter. More blood determinations would have been of value, but patients objected to more frequent venipuncture. Collections of milk, blood and urine

were continued, for two or more days after the drug had been discontinued, i.e., a total of at least five days. The levels of both free and acetylsulfanilamide in the blood and milk were compared and the total amounts of the drug excreted in the milk and urine were determined.

The method for determination of free and conjugated sulfanilamide in the blood and urine was that described by Marshall<sup>3</sup> with the improvement recently suggested by him<sup>4</sup>; namely, the use of buffered ammonium sulfamate for the destruction of the excess nitrous acid. This modification has greatly improved the original method and makes for a much better color match. The method for the determination of free sulfanilamide excreted in the milk was the same as that described by us<sup>1</sup> earlier except that the dilution was 1:10 instead of 1:5, and the buffered ammonium sulfamate was incorporated. The procedure was briefly as follows:

To 5 c.c. of milk in a centrifuge tube was added 2.5 c.c. of a 20 per cent solution of p-toluenesulfonic acid. The solutions were mixed, allowed to stand overnight at room temperature, and then centrifuged and filtered. One and one-half cubic centimeters of the clear supernatant liquid was pipetted into a flask and diluted with 9 c.c. of distilled water and 0.5 c.c. of p-toluenesulfonic acid. To this solution was added 1 c.c. of a 0.1 per cent solution of sodium nitrite and after three minutes, 1 c.c. of a 1 M solution of sodium dihydrogen phosphate containing 0.5 per cent of ammonium sulfamate ( $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ , 13.8 gm., ammonium sulfamate 0.5 gm.). After two minutes 5 c.c. of a solution of dimethyl  $\alpha$  naphthylamine (1 c.c. in 250 c.c. of 95 per cent ethyl alcohol) was added. After fifteen to thirty minutes the colors were compared with a suitable standard. Ordinary breast milk to which definite concentrations of sulfanilamide had been added and then treated in the manner just described was used as a standard.

In order to determine the acetylsulfanilamide, a 1:20 dilution was used. To 1.5 c.c. of the clear supernatant liquid was added 15 c.c. of water and 3.5 c.c. of p-toluenesulfonic acid and the solution heated in a boiling water bath for ninety minutes. The standard was heated in the same manner. The solutions had a faint brownish tinge, but since the standard was treated in the same way, it was not difficult to get a good color match. After the solutions had cooled, the procedure was the same as that for the determination of free sulfanilamide except that a 2 M buffer containing 0.5 per cent ammonium sulfamate was used instead of the 1 M buffer.

The 25 patients studied have been divided into three groups, depending upon the amount of drug received (Table I).

TABLE I. DIVISION OF PATIENTS ACCORDING TO SULFANILAMIDE DOSAGE

GROUP	NO. PATIENTS	SINGLE DOSE	DAILY DOSE	TOTAL DOSE
		GM.	GM.	GM.
I	10	0.35* ( 5 gr.)	2 (30 gr.)	7.33 (110 gr.)
II	5	0.66 (10 gr.)	4 (60 gr.)	12.00 (180 gr.)
III	10	0.80 (12.5 gr.)	5 (75 gr.)	15.00 (225 gr.)

\*In order to reach the desired blood level rapidly, these patients received 0.66 gm. (10 gr.) each for the first four doses.

Chart 3 compares the excretion of the right and left breasts separately. Milk was obtained every four hours, but since the breasts were pumped alternately, the determination for each specimen was a level for the preceding eight hours. As can be seen the general direction of the curve for each breast was very similar, but there was a slight lag of one breast behind the other.

Charts 4, 5, and 6 compare the free and total sulfanilamide (free plus acetyl) in the blood and milk of a typical patient from each of

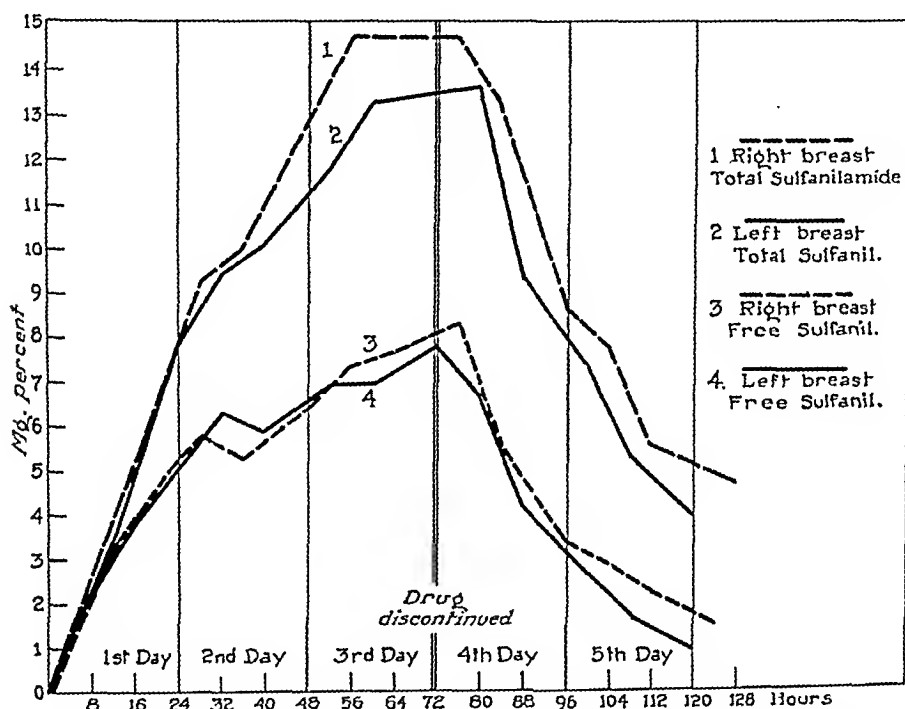


Chart 3.—Comparison of the excretion of the sulfanilamide by the right and left breasts.

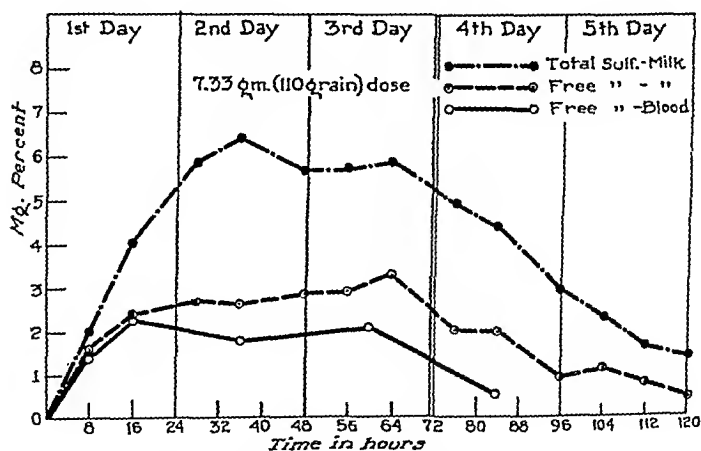


Chart 4.—Comparison of the free and total sulfanilamide (free plus acetyl) levels in the milk and blood. Dose 7.33 gm. (110 gr.).

the three groups studied. The comparison was made over a period of five days; three days during which the drug was administered and two days following. The blood level had usually been established within twenty-four hours and so a comparison of the second and third days should be fairly accurate.

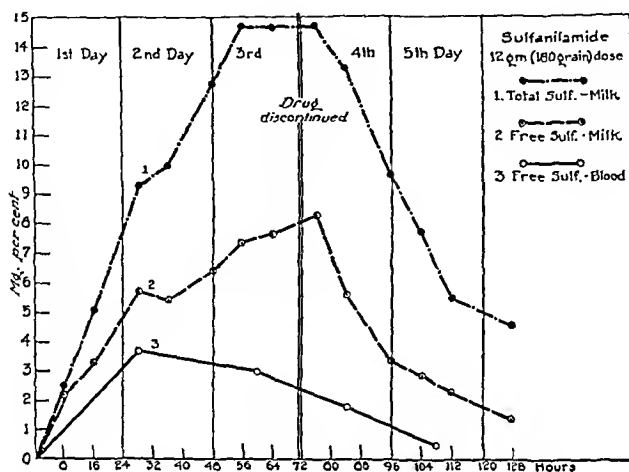


Chart 5.—Comparison of the free and total sulfanilamide levels in the milk and blood. Dose 12.0 gm. (180 gr.).

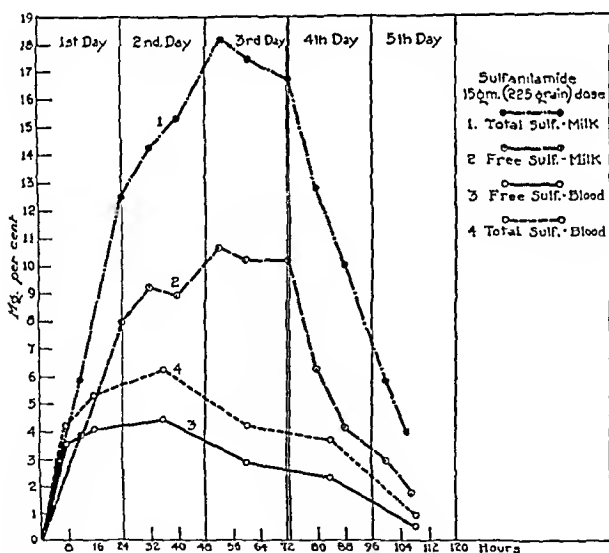


Chart 6.—Comparison of the free and total sulfanilamide levels in the milk and blood. Dose 15.0 gm. (225 gr.).

As in the series previously reported, it was noted that the free sulfanilamide level in the milk was considerably higher than that in the blood. In fact, in most cases it was at least twice as great, and with large doses seemed to be considerably more than twice. The total (free plus acetyl) level was still much higher. Table II shows this quite clearly.

TABLE II. A COMPARISON OF THE VARIATION IN THE PEAKS OF THE SULFANILAMIDE LEVELS IN THE BLOOD AND MILK (MG. PER 100 C.C.)

GROUP	NO. PATIENTS	DAILY DOSE	FREE IN BLOOD	FREE IN MILK	TOTAL IN MILK*
I	10	2 gm.	2.15-2.50	2.97- 5.27	5.29- 9.25
II	5	4 gm.	1.78-3.70	6.25-14.70	10.50-22.41
III	10	5 gm.	3.24-7.68	6.28-16.66	9.25-28.57

\*Free plus hydrolyzed acetyl.

Just why there was such a difference in the levels in the milk and blood cannot be explained, although the differences may not be as great as the graphs might lead one to believe. The milk and blood specimens were collected at the same time, but it cannot be assumed that the time relationship of the levels is absolute. The blood level is momentary, while the milk level may possibly represent a cumulation level for the previous eight hours.

A short time ago, Stewart and Pratt<sup>5</sup> reported their study of the excretion of free sulfanilamide in 28 normal convalescent women during the first eight post-partum days. Ten of their patients received 2 gm. (30 gr.) of sulfanilamide daily, and 18 received 4 gm. (60 gr.). From single daily blood and milk determinations, they concluded that in those who received 2 gm., "the concentration of free sulfanilamide in the breast milk corresponded closely to the estimations in the blood stream (2 to 4 mg. per 100 c.c.)." In those who received 4 gm., "the concentration of the blood showed greater variation (4 to 7 mg. per 100 c.c.) and the concentration in the milk was generally equal to or slightly higher than the blood." Their blood concentrations agree quite well with both our earlier and present observations with similar dosages, but we have consistently found the milk level to be considerably higher than that of the blood. This discrepancy may be due to the difference in the method of determination of the drug in milk.

Recently, Pinto<sup>6</sup> has reported determinations on 3 patients over a period of twenty-four hours. The levels in the milk were in agreement with ours. He gave no data on blood determination, but made the statement that "the concentrations of sulfanilamide in human milk after the ingestion of a single large dose of the drug, follows a course similar to that found by other workers for its concentration in the blood. The only difference is that the peak concentration in milk seems to lag behind that in the blood by several hours."

Since an appreciable amount of the drug was excreted in the milk in the acetyl form, it was of interest to determine whether there was any: Relationship between the percentage conjugated and (1) the amount of drug ingested; (2) the amount of drug excreted; (3) the volume of milk secreted; (4) the period in the course of the treatment.

From Chart 7, it can be seen that in the milk, blood and urine, the peaks for the excretion of the total sulfanilamide (free plus hydrolyzed acetyl) paralleled the free sulfanilamide peaks. Considering the individual variation in the absorption and excretion of this drug and its dependence upon fluid intake, correlation of the data on a

small number of patients is difficult. The relationship between the percentage of drug conjugated and the amount of drug ingested and excreted can best be observed from Table III, which gives the variations noted in each group of patients.

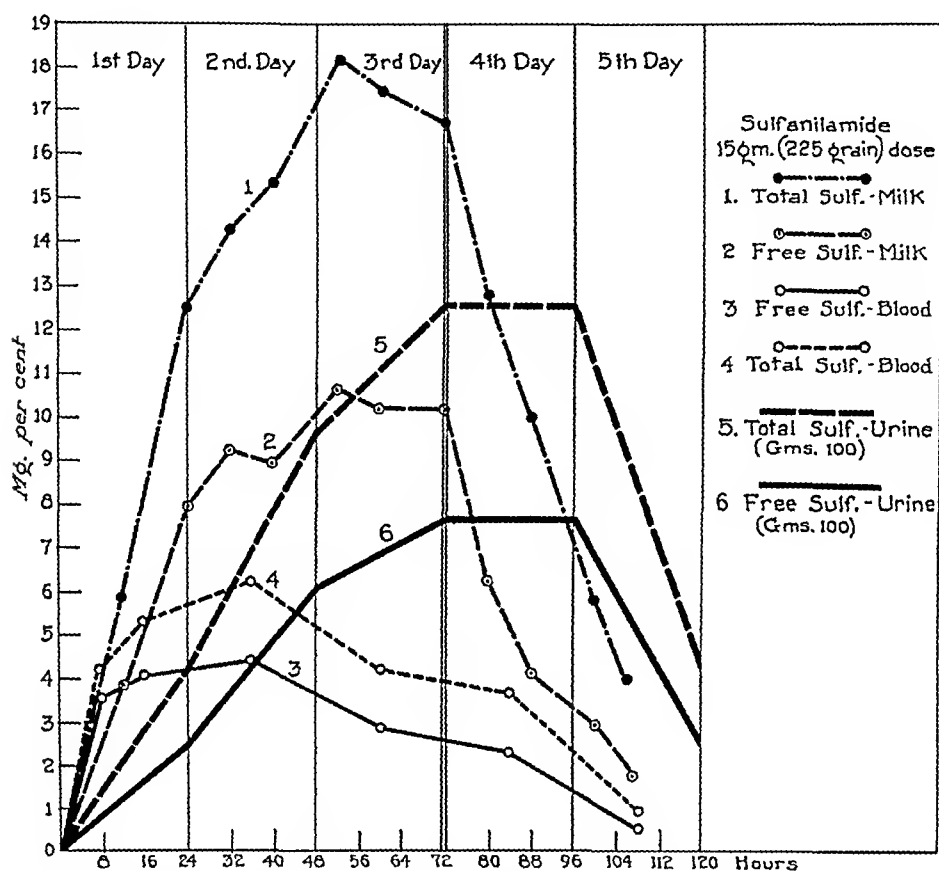


Chart 7.—Comparison of the free sulfanilamide peaks with the total sulfanilamide peaks in blood, milk and urine.

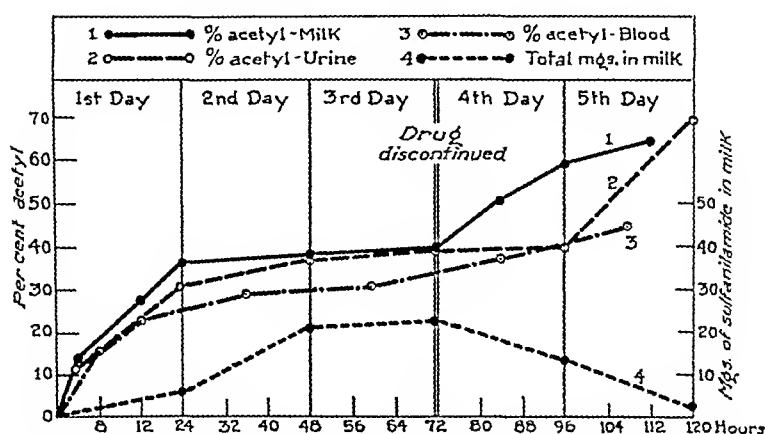


Chart 8.—Comparison of the percentage of the drug conjugated in the blood, milk, and urine during the course of the treatment.



Toward the end of the course of observations of the patients, i.e., during the fourth and fifth days when therapy had been discontinued and the amount of drug excreted was gradually decreasing, there was a sharp rise in the percentage of the drug conjugated (Chart 8).

The higher percentage conjugated toward the end of the course cannot be dependent upon the smaller total amount being excreted then, because there was only a relatively small amount being excreted at the beginning of the experiment when the percentage of acetyl was low. It would appear that if there was any storage of the drug in the body it was stored as the acetyl, or, at least, that the last traces of the drug were excreted as the acetyl derivative. In this respect it would be of interest to observe the percentage of acetyl excreted in the urine of patients with impaired renal function.

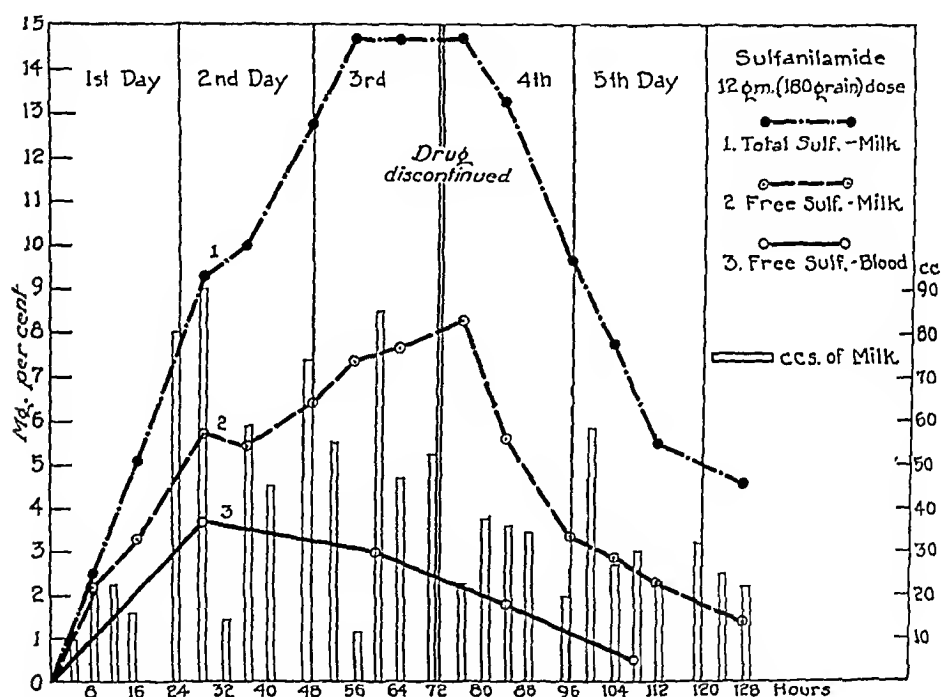


Chart 9.—Comparison of the concentration of the drug excreted with the volume of milk secreted.

Chart 9, of a patient typical of Group III, shows the relationship between the concentration of sulfanilamide in the milk and the volume of milk secreted. The variation in the amount of milk obtained at the 56-, 60-, 64-, 72- and 76-hour collections was from 12 to 87 c.c., yet the sulfanilamide level (free plus conjugated) remained constant at 14.7 mg. per 100 c.c. That is, if after the peak sulfanilamide level in the milk had been reached, the level in the blood were maintained fairly constant, the concentration per cubic centimeter of the drug in the milk remained the same whether the total volume of the milk were large or small. Further studies of this type might lead to a better knowledge of the mechanism of lactation.

TABLE III. THE RELATIONSHIP BETWEEN THE AMOUNT OF DRUG CONJUGATED AND THE AMOUNT OF DRUG INGESTED, THE AMOUNT OF DRUG EXCRETED AND THE VOLUME OF MILK SECRETED

GROUPS	PATIENTS	TOTAL DOSE	EXCRETED IN MILK	MG. PER C.C.	TOTAL DOSE PER CENT	EXCRETED AS ACETYL
A	10	2.00 gm.	3.7- 13.7 mg.*	0.006-0.02		
B	10	4.00 gm.	11.8- 54.0 mg.*	0.02 -0.04		
I	10	7.33 gm.	38.7- 93.4 mg.	0.04 -0.07	0.53-1.23	35.11-60.99%
II	5	12.00 gm.	50.3-166.4 mg.	0.07 -0.18	0.45-1.40	35.34-46.00%
III	10	15.00 gm.	64.5-233.3 mg.	0.11 -0.20	0.45-1.62	45.16-83.98%

\*Free sulfanilamide only.

No severe toxic symptoms were observed in any of our patients, but many of them became cyanotic. Many pediatricians feel that children tolerate the drug as well, if not better, than adults. Not much is known yet concerning the tolerance or later effects of the drug in the newborn. Helmholz<sup>8</sup> prescribed a dose of 0.33 to 0.50 gm. per day for infants. In the treatment of infants ill with meningococcus infection, Waghelstein<sup>9</sup> used a daily dose calculated on the basis of 250 mg. per kilogram of body weight. Long and Bliss<sup>10</sup> estimated that in severe infections, 1 gm. of sulfanilamide per 10 pounds of body weight should be received during the first twenty-four hours.

The largest amount of drug excreted in the milk in any case (Table III) was only 0.23 gm., 1.62 per cent of the total dose ingested, and that was in a patient whose blood level was 5 mg. per 100 c.c. It is quite difficult to maintain a blood level higher than this in patients without impaired renal function or without limitation of fluids.<sup>11</sup> Most patients in whom it is desirable to maintain a blood level higher than 5 mg. per 100 c.c. would probably be so ill that the baby would be removed from the breast anyway. None of the babies in our experiments were breast fed, but in the work of Stewart and Pratt<sup>5</sup> they were permitted to nurse. They observed no toxic manifestations in the babies.

In our previous paper we suggested that until more was known of the tolerance of the newborn for the drug, and until further work had been done upon the excretion of sulfanilamide during therapeutic dosage, breast feeding be discontinued during the period that the drug was being excreted in the milk. The present study has shown that an increased dose of sulfanilamide administered over a prolonged period does not greatly increase the percentage of the drug excreted, and since the total amount of drug excreted over a period of five days was never greater than 0.23 gm., it would seem that there is probably little danger to a nursing infant unless it is unusually susceptible to sulfanilamide.

#### CONCLUSIONS

1. Sulfanilamide has been administered to 25 lactating women in therapeutic doses over a period of three days, and the free and acetyl-sulfanilamide levels determined in the blood, milk, and urine.

2. A method has been devised for the determination of free and acetylsulfanilamide in milk.

3. The level in the milk was considerably higher than that in the blood.

4. The drug was still being excreted in the milk in measurable, but negligible, amounts forty-eight hours after administration had been discontinued.

5. The percentage of the sulfanilamide excreted in the conjugated acetyl form was relatively low the first day the drug was administered, increased slightly the second and third days, and rose sharply the fourth and fifth days when administration of the drug had been discontinued. The percentage varied from 35.1 to 83.9. The same general course was observed in blood and urine.

6. After a fairly constant blood level had been established, the drug seemed to be excreted in the milk at a definite concentration per cubic centimeter rather than per total volume.

7. The total amount of sulfanilamide excreted in the milk over a period of five days was never greater than 0.23 gm., 1.6 per cent of the total dose ingested.

8. With the dosages used in these experiments, the amount of drug excreted in the milk was so small that there probably would be little danger to the nursing infant unless it was unusually susceptible to sulfanilamide.

The sulfanilamide (prontolin) was supplied by the Department of Medical Research of the Winthrop Chemical Co., Inc.

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**Smith, Earl C.**: The Use of Camphor-In-Oil to Check Lactation, New Orleans Med. Surg. J. 91: 127, 1938.

The author has used intramuscular injections of 3 gr. of camphor-in-oil to check lactation, when indicated, in 115 patients. When the patients were started on this treatment within the first twenty-four hours post partum, 85 to 95 per cent did not develop second degree engorgement. Even after the first twenty-four hours, the usual length of time that a woman suffers from "increased mammary tension" is shortened. No unfavorable reactions were noted. Smith advises injections twice daily for the first two days and once on succeeding days. His average total dosage per patient was 5.1 or 16 gr.

EUGENE S. AUER.

## A PRELIMINARY REPORT ON THE USE OF SULFANILAMIDE IN PUERPERAL AND POSTABORTAL INFECTIONS\*

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FOLLOWING Domagk's<sup>1</sup> demonstration of the bactericidal effects of the azo-sulfamido compounds in the treatment of hemolytic streptococcus infections in mice, Levaditi and Vaisman<sup>2</sup> and Trefouel and others,<sup>3</sup> of France also demonstrated their effectiveness in experiments on mice. In their researches they stressed the prophylactic rather than the curative value. Then followed the work of LaComme<sup>4</sup> who used the drug prophylactically giving it with satisfactory results to patients the day following delivery. Colebrook and Kenny in 1936<sup>5</sup> and Colebrook and Purdie<sup>6</sup> in 1937 reported on their use of prontosil and sulfanilamide in the treatment of hemolytic streptococcus puerperal infection with striking results. Early in its use sulfanilamide was thought to be of value only in beta hemolytic streptococcus infections, but more recent work has demonstrated its value in infections caused by other organisms such as gonococci,<sup>7</sup> meningococci,<sup>8</sup> organisms commonly found in infections of the urinary tract,<sup>9, 10</sup> pneumococci,<sup>11</sup> staphylococci<sup>12</sup> and *Bacillus welchii*.<sup>13</sup>

In order to achieve its full bactericidal effect sulfanilamide must be given early in sufficient amounts to create a concentration of approximately 10 mg. per 100 c.c. of blood. Long and Bliss<sup>14</sup> have demonstrated that this amount is effective. To establish this concentration it is recommended that approximately 1 gm. per 20 pounds of body weight be given in twenty-four hours, although occasionally in fulminating infections larger doses may be used. Sulfanilamide is absorbed from the gastrointestinal tract in approximately four hours, and it then passes readily from the blood stream and is widely distributed throughout the tissues. In the administration of daily divided doses of the drug an average of two to three days is required to establish an equilibrium between the amount ingested and the amount excreted in the urine; a similar interval is necessary to free the body of the substance. It is excreted practically entirely in the urine in a free state and in a conjugated form (probably as para-acetyl-aminobenzenesulfonamide).<sup>15</sup> In cases of impaired renal function caution must be used in the administration of sulfanilamide in order to avoid too high a blood concentration. Subcutaneous administration does not lead to a higher concentration in the blood than the oral administration, and it has seemed to us that the latter method is preferable. If this is impossible due to nausea or vomiting or the inability of

\*Presented at a meeting of the Chicago Gynecological Society, December 16, 1938.

This is only a preliminary report. Further work is in progress and in a later report I will present observations on a larger series of cases to determine the effectiveness of sulfanilamide in puerperal and postabortal infections.

the patient to take anything by mouth, sulfanilamide administered subcutaneously or prontosil solution intramuscularly may be employed. Sulfanilamide can also be administered per rectum if necessary, although we have had no occasion to do so. Sulfanilamide is relatively insoluble, but an 0.8 per cent solution in normal saline can be made up and given by hypodermoclysis when necessary. This solution is administered soon after preparation because of its tendency to crystallize below 37° C.<sup>14</sup>

The question of dosage is difficult to outline rigidly and should depend upon the clinical condition of the patient. Our practice is to continue the original dosage until a definite improvement in the patient's condition has been noted. In most cases we have given 90 gr. per day for at least three days, and at the end of this time the dosage is reduced to 60 gr. per day if the patient has shown improvement. As improvement continues it is reduced to 30 gr. daily. It should not be discontinued before the temperature has been normal unless complications result. We have found it possible to continue this dose for three to four weeks if necessary. In order to combat the possibility of acidosis due to the sulfanilamide, we concurrently administer sodium bicarbonate 10 to 20 gr.

Since sulfanilamide has been found to be of value in numerous infections besides those caused by the hemolytic streptococcus, we have treated every alternate case of puerperal and postabortal infection with sulfanilamide and have used the nontreated cases as controls. On admission cervical cultures were taken in all cases.

In this study puerperal infection will be considered as an acute infection of the female generative tract producing an acute inflammation of the uterus or its surrounding structures, peritoneum, or blood stream. Extragenital tract infections occurring in the puerperium were not included in this series. All patients treated were in the obstetric infection ward of Cook County Hospital having been delivered in the hospital or elsewhere. Every case of morbidity having a temperature of 100.4° F. on two occasions or 101° F. on one occasion after the first twenty-four hours was included, and a similar temperature elevation was used in the case of postabortal infections. The modern accepted conservative treatment of puerperal infection was carried out in all cases and blood transfusions were freely resorted to where indicated. The patients treated with sulfanilamide were given this drug in addition to the above measures.

Tables I to VII summarize our results. We have classified the various infections into four types on a clinicopathologic basis similar to the classification of Colebrook.<sup>12</sup>

- Type I: In which the infection is limited to the uterus, vagina or perineum
- Type II: In which the infection involves the pelvic cellular tissues, tubes, pelvic peritoneum or veins
- Type III: Associated with a generalized peritonitis
- Type IV: Associated with a septicemia

All cases of puerperal infection and postabortal infection should be considered as serious, but to aid in describing them we have further

classified the cases into severe and mild. We describe a severe case as one in which the patient has a fever for eight days or more or 102° F. on two days or more.

TABLE I

Puerperal infection cases	105	Control	55	Sulfanilamide	50	W-40	C-65
Postabortal cases	99	Control	52	Sulfanilamide	47	W-69	C-30
Total	204		107		97		

TABLE II. TYPE I LIMITED TO THE UTERUS, VAGINA OR PERINEUM

	CASES	MILD	SEVERE	TOTAL DAYS FEVER	AVER. DAYS FEVER	DIED	PER CENT MORTAL- ITY
Puerperal Infection:							
Control	48	35	13	353	9.4	0	10
Sulfanilamide	50	24	16	194	4.8	0	0
Postabortal Infection:							
Control	36	21	15	192	5.3	0	0
Sulfanilamide	31	14	17	203	6.5	0	0

TABLE III. TYPE II INVOLVING PELVIC CELLULAR TISSUES, TUBES, PELVIC PERITONEUM OR VEINS

	CASES	MILD	SEVERE	TOTAL DAYS FEVER	AVER. DAYS FEVER	DIED	PER CENT MORTAL- ITY
Puerperal Infection:							
Control	6	0	6	110	18.0	0	0
Sulfanilamide	8	1	7	137	17.0	0	0
Postabortal Infection:							
Control	8	2	6	97	12.0	1	12.5
Sulfanilamide	12	1	11	107	8.8	0	0

TABLE IV. TYPE III ASSOCIATED WITH GENERALIZED PERITONITIS

	CASES	MILD	SEVERE	TOTAL DAYS FEVER	AVER. DAYS FEVER	DIED	PER CENT MORTAL- ITY
Puerperal Infection:							
Control	0	0					
Sulfanilamide	0	0					
Postabortal Infection:							
Control	3	0	3	15	5.0	3	100
Sulfanilamide	2	0	2	37	18.5	1	50

TABLE V. TYPE IV ASSOCIATED WITH SEPTICEMIA

	CASES	MILD	SEVERE	TOTAL DAYS FEVER	AVER. DAYS FEVER	DIED	PER CENT MORTAL- ITY
Puerperal Infection:							
Control	1	0	1	24	24	1	100
Sulfanilamide	2	0	2	48	24	2	100
Postabortal Infection:							
Control	5	0	5	91	18	3	60
Sulfanilamide	2	0	2	26	13	0	0

TABLE VI. SUMMARY

	CONTROL	55 CASES	1 DEATH	MORTALITY 1.8%
Puerperal Infection Cases	Type I	48 cases	Deaths 0	
	Type II	6 cases	Deaths 0	
	Type III	0 cases	Deaths 0	
	Type IV	1 case	Deaths 1	
	Total	55	1	
	SULFANILAMIDE	50 CASES	2 DEATHS	MORTALITY 4%
Puerperal Infection Cases	Type I	40 cases	Deaths 0	
	Type II	8 cases	Deaths 0	
	Type III	0 cases	Deaths 0	
	Type IV	2 cases	Deaths 2	
	Total	50	2	
	CONTROL	52 CASES	7 DEATHS	MORTALITY 13.4%
Postabortal Cases	Type I	36 cases	Deaths 0	
	Type II	8 cases	Deaths 1	
	Type III	3 cases	Deaths 3	
	Type IV	5 cases	Deaths 3	
	Total	52	7	
	SULFANILAMIDE	47 CASES	1 DEATH	MORTALITY 2.1%
Postabortal Cases	Type I	31 cases	Deaths 0	
	Type II	12 cases	Deaths 0	
	Type III	2 cases	Deaths 1	
	Type IV	2 cases	Deaths 0	
	Total	47	1	

TABLE VII. SUMMARY OF MORTALITY

	TOTAL CASES	MORTALITY	PER CENT MORTALITY
Control			
Puerperal infection	55	1	
Postabortal infection	52	7	
	107	8	7.4%
Sulfanilamide			
Puerperal infection	50	2	
Postabortal infection	47	1	
	97	3	3.09%

## COMPLICATIONS

To prevent certain toxic effects and serious consequences of the administration of this drug, close observation is necessary. Failure to exercise this attention may lead to definite ill effects. We feel that all patients receiving large doses of sulfanilamide should be hospitalized and kept under close observation. It is thought that in some instances the toxic effects are due to an idiosyncrasy<sup>16</sup> rather than to the drug itself. We have had no fatalities from sulfanilamide per se nor have we noted any renal or hepatic damage. Close observation of patients under treatment and familiarity with untoward reactions should permit detection of such reactions early enough to obviate serious trouble.

It is not always easy to differentiate between the mild toxic symptoms of the drug and symptoms due to the infection. The toxic effects we have observed are malaise, headache, nausea, anorexia, vertigo; these are seen frequently, but they usually pass off rapidly. Numbness and tingling of the extremities occur in a few cases and diarrhea is also observed in some instances. Fever has been reported as one of the toxic manifestations,<sup>14</sup> but in puerperal infection it is difficult to distinguish between a rise in temperature due to a change in the patient's condition or to the drug. When due to the drug the temperature rapidly subsides on withdrawal of medication.

Cyanosis of varying degree is observed in a large number of patients undergoing intensive treatment. Formerly it was thought to be due to sulfhemoglobinemia or methemoglobinemia,<sup>12</sup> but the amount of methemoglobin and sulfhemoglobin found in the blood is too small to explain the intense cyanosis, and it has been shown that it may be unaccompanied by any decrease in the oxygen carrying power of the blood. It is now thought that the cyanosis is due to the presence of an oxidation product<sup>17</sup> rather than to methemoglobin or sulfhemoglobin. Early in our use of sulfanilamide we discontinued it when we noted cyanosis; we do not do so for mild cases at present. Patients on sulfanilamide therapy should not be given magnesium sulfate as a laxative nor should they be given foods containing sulfur. Patients suffering from severe infections frequently become anemic, and it is difficult to determine whether the anemia is due to the infection or to the drug. When due to sulfanilamide severe headache and dizziness frequently precede the onset of anemia. Anemia which we thought probably due to sulfanilamide occurred in 3 of the 97 patients treated or slightly over 3 per cent which corresponds to the percentage reported by W. Barry Wood of Baltimore.<sup>18</sup>

Immediate withdrawal of the drug in cases of anemia may be sufficient in mild cases; blood transfusion is satisfactory in severe cases. A mild skin rash occurred in two of our cases. Deafness occurred in one case, but cleared upon withdrawal of the drug; to my knowledge this is the first case reported. Agranulocytosis occurred in one of our cases. A patient with a Type I postabortal infection, who was admitted on June 14, 1938 and was discharged on July 18, had a severe infection with six days of temperature of 103° F. and seven days of 101° F. before the development of agranulocytosis. Her red blood count on admission was 2,910,000; white blood count 16,100. A blood transfusion of 500 c.c. on June 21 was given for her anemia; on July 7 the blood count was Hb 60 per cent; red blood cells 3,590,000; white blood cells 1,800 with a typical agranulocytic differential count. A transfusion was given that day. The white count dropped to 450 on July 8 and another transfusion was given on July 10 with immediate white cell improvement to 3,500 which subsequently rose to normal and on discharge from the hospital her Hb was 67 per cent; red blood count 4,220,000 and white blood count 8,800.

Early mild toxic symptoms usually do not require any treatment, but they should put one on guard against more severe reactions. In all cases



of severe reactions the drug should be stopped and fluids forced since the drug is rapidly and practically completely eliminated in the urine.

It is evident that the great majority of patients with puerperal infection fall under the Type I classification. This corresponds to Colebrook's series<sup>12</sup> and other reports.<sup>19</sup> Since practically all the patients with localized infections survive, we feel that we have not had a sufficient number of cases of generalized infection to arrive at definite conclusions in this preliminary study.

Two patients from whom hemolytic streptococci were cultured on control treatment died; in none of the sulfanilamide treated patients who died were hemolytic streptococci found. We do feel, however, that sulfanilamide has reduced the number of days of fever in the Type I and II cases; it probably has prevented some of these infections from becoming generalized.

The difference in the mortality percentage between the control and the sulfanilamide group can very well be accounted for by the increased number of cases of Type III and IV in the control series. We plan to continue this work, and we hope, with a larger series of cases, to be able to arrive at more definite conclusions. We feel that if chemotherapy is to be of value, treatment should be instituted early. Also we should not expect striking results in cases with far-advanced infections or in those who are moribund on admittance. Since sulfanilamide has toxic effects which may be serious if not discovered, we feel that all patients should be under close observation.

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The authors ascertained that arsphenamine can be demonstrated in the organs of the pregnant organism, in the decidual vessels and in the intervillous spaces, but not in the chorion or in the fetal organs. Since the independent defense of the fetus against a syphilitic infection is inadequate as the result of the impermeability of the chorion, it is important that energetic treatment is begun before or at the beginning of the pregnancy.

J. P. GREENHILL,

# USE OF A SULFANILAMIDE DERIVATIVE IN THE TREATMENT OF GONORRHEA IN PREGNANT AND NONPREGNANT WOMEN\*

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THE work of Long<sup>1</sup> at Johns Hopkins on the use of sulfanilamide in the treatment of streptococcal infections and especially the results obtained by Colebrook and Kenny<sup>2</sup> in the use of sulfanilamide in puerperal sepsis, have stimulated widespread interest in its clinical application to various gynecologic affections.

The excellent results reported by Dees and Colston,<sup>3</sup> Herrold,<sup>4</sup> Cokinnis,<sup>5</sup> and others<sup>6, 7, 8</sup> in treating gonorrhea in males and by Carey,<sup>9</sup> Hageman<sup>10</sup> and Hoffman, Schneider, Blatt and Herrold<sup>11</sup> in gonorrheal vulvovaginitis of children, direct attention to the possible value of this drug in gonorrheal infections of adult women.

We determined to study its effect on various types of gonorrheal infection in adult women, evaluating its clinical results by the use of smears, gonorrheal complement-fixation tests, and the change in clinical symptoms occurring after the use of the drug.

The exact mechanism of the action of sulfanilamide and its derivatives on the gonococcus has as yet not been determined, although numerous experimental studies of that question have been conducted. The consensus of opinion seems to be that the effect on the gonococcus is one of bacteriostasis with some small degree of bactericidal action.<sup>2, 12-14</sup> Many believe also that a change is produced in the leucocytes rendering them more effective in overcoming the infection. However, the work of Osgood,<sup>15</sup> of Welch, Wentworth, and Mickle,<sup>16</sup> and of Coman,<sup>17</sup> seem to disprove this since they could demonstrate no chemotropic or opsonic changes. The work of Casper<sup>18</sup> has shown that culturing gonococci in media to which one of the sulfanilamide drugs has been added produces degenerative changes as shown by variations in morphology and size of the colonies produced.

Various derivatives of sulfanilamide having similar effects have been produced by combining azo dyes with the sulfanilamide grouping and by forming various complex organic salts. A discussion of the exact chemical composition and structure is obviously beyond the scope of a purely clinical report of this type and for that reason we refer those interested to other publications such as those of Domagk,<sup>19</sup> Levaditi and Vaisman,<sup>20</sup> and others.

\*Presented at a meeting of the Chicago Gynecological Society, December 16, 1938.

The drugs of the sulfanilamide group are all readily and completely absorbed from the gastrointestinal tract. Following administration, sulfanilamide has been detected in the prostatic secretion,<sup>21</sup> cervical secretion,<sup>22</sup> the breast milk,<sup>23</sup> and the secretions of various glands.

Neoprontosil, the drug used in the majority of our cases, is the disodium salt of the combination of an Azo dye with sulfanilamide (disodium 4, sulfamido phenyl 2, Azo 7, Acetyl amino 1, hydroxynaphthalene 3, 6 disulfonate). Its pharmacologic properties are similar to those described for sulfanilamide by Bröwn, Bannick, and Foster,<sup>24</sup> Rosenthal,<sup>25</sup> and Barlow<sup>26</sup> have shown that its toxicity is lower and that it may be administered successfully to patients who previously had been unable to tolerate sulfanilamide because of severe toxic reactions.

Because of the many toxic reactions reported with sulfanilamide, it was decided to study the value of smaller doses given in interrupted courses over short periods. Osgood,<sup>16</sup> Herrold,<sup>14</sup> and Long<sup>12</sup> have stated that in nonfulminating infections such as gonorrhea, small doses seem to be more effective and less dangerous. Our patients were, therefore, given the drug in courses consisting of 40 gr. daily for periods of five days, in 10 gr. doses taken orally after meals and before bedtime.

These patients were from the Out-Patient Venereal Gynecological Dispensary of the Illinois Research and Educational Hospital. No attempt was made to select the cases. No patient was given the drug unless she had both positive smears and clinical evidence of gonorrhea. No local or other form of treatment was used with the sulfanilamide.

After routine urinalysis, blood pressure, and gonorrhea complement-fixation test, the patient was given the drug (in capsules or tablets of gr. v each) and told to take 40 gr. daily, 10 gr. after each meal and 10 gr. at bedtime for five days. She was told about toxic manifestations and warned to discontinue the drug if severe symptoms appeared. Alcohol and sexual activities were interdicted. Patients with Bartholinitis were given hot sitz baths.

The diagnosis was established by finding gonococci in urethral and cervical smears stained by Gram's method, almost all of which were examined by one of us; and by clinical signs and symptoms. No patient was considered cured unless all signs and symptoms of gonorrhea had cleared up and at least three consecutive negative urethral and cervical smears were obtained.

All of our cases were ambulatory, and were seen once weekly. After finishing a five-day course of treatment, the patient was examined clinically and bacteriologically at the next weekly visit. If she showed no further evidence of infection she was observed at subsequent weekly visits until a cure was definitely established. If, after one course, the patient still showed evidence of infection another course of medication was begun on the visit one week later. This procedure was followed until cure or failure was definitely established. After the patients were considered cured they were told to return to their nor-

mal mode of life and were then seen at gradually lengthened intervals for periods up to eight months. The pregnant patients were followed until six weeks to eight weeks after delivery and the condition of the baby was inquired into in each case. Thus, all patients except two or three uncooperative individuals were observed for periods ranging from three to eight months for evidences of relapse or incomplete cure.

There were 45 cases studied, of which 39 were chronic gonorrhea, 3 subacute, and 3 acute. There were 22 white women and 23 colored women in the series, and their ages ranged from 15 to 38 years. Nineteen of our patients were pregnant, the duration of pregnancy ranging at the time of treatment from the third to the ninth month and included both primiparas and multiparas. All degrees of gonorrheal involvement were present in this series, including urethral, Skene's vaginal, cervical, Bartholin's glands, parametrial and adnexal. There was one case complicated by arthritis and another by a mycotic vaginitis. Thirteen of the patients had been previously treated for variable lengths of time. Of the 45 patients treated, 44 were cured. One was improved but not cured.

As shown in Table I, 26 cases showed negative smears at the end of one week, 9 at the end of two weeks, 1 at the end of four weeks, and 1 at the end of four days. In 5 cases the exact time at which the smear became negative was not determined, because the patients failed to keep their appointments and returned three to ten weeks after taking the drug, at which time they were found negative, so that we were able to assume they had become negative in the interim.

TABLE I. TIME REQUIRED TO BECOME SMEAR NEGATIVE

TIME REQUIRED	4 DAYS	1 WEEK	2 WEEKS	4 WEEKS	EXACT TIME UNDETERMINED	APPROX. AVERAGE TIME
No. of cases	1	29	9	1	5	1.06 wk.

The time required to establish complete cure varied, with the severity of the disease, the degree of involvement, the duration of infection at the time treatment began, and the individual response to neoprontosil. Our figures in this respect are longer than the time actually required for cure because of our method of observing the patient for a week following each five-day course of the drug. In general, acute cases and pregnant women with minimal involvement responded most rapidly, while chronic cases with extensive adnexal pathology responded more slowly. Eleven patients were completely cured at the end of two weeks, 6 at the end of three weeks, 8 in four weeks, 6 in five weeks, 3 in six weeks, 1 in seven weeks, 1 in eight weeks, and 2 in nine weeks. In 6 patients the exact time of cure was not determined. These figures are summarized in Table II.

TABLE II. TIME REQUIRED TO OBTAIN COMPLETE CURE

TIME REQUIRED FOR CURE	2 WK.	3 WK.	4 WK.	5 WK.	6 WK.	7 WK.	8 WK.	9 WK.	EXACT TIME UNDETERMINED
No. of cases	11	6	8	6	3	1	1	2	6

The number of five-day courses of the drug required for cure varied with the degree of involvement. Twenty patients were cured by one

course; 13 required 2 courses; 8 required 3 courses; 2 patients received 4 courses before cure was obtained; and 1 patient required 6 courses, as shown in Table III. Seventy-three per cent of our patients were cured by one- or two- or five-day courses of sulfanilamide.

TABLE III. NUMBER OF COURSES OF SULFANILAMIDE REQUIRED FOR CURE

NO. OF COURSES OF SULFANILAMIDE REQUIRED FOR CURE	1	2	3	4	6
No. of cases	20	13	8	2	1

In general, the pregnant women responded more favorably than the nonpregnant. In no instance was a gonorrheal puerperal sepsis noted in spite of the fact that none of the patients was under active treatment at the time of delivery. All patients were discharged from the hospital by the tenth day. There was no instance of renal irritation caused by the drug since none of the patients developed albuminuria or toxic symptoms. Only one patient required treatment during lactation and in this instance no gastrointestinal disturbance was noted in the baby.

Re-appearance of signs of gonorrheal infection, such as the return of vaginal discharge or of positive smears showing a few scattered organisms, was noted in fourteen cases. Of these, all but one admitted re-exposure with the same partner who had originally infected her. In each of these cases the patient had been showing negative smears and had been entirely free from symptoms for periods of from two to eight weeks at the time symptoms were again seen. Because these patients admitted exposure with infected partners, because we had no supervision over our patients outside of the clinic, and because a large percentage of these women were of a type which would not obey any orders relative to sexual abstinence, we feel that we can safely regard these cases as re-infections rather than recurrences or relapses.

One patient who had repeated relapses admitted after prolonged questioning that the relapses followed soon after re-exposure with the same partner on each occasion. In spite of several reinfections in her case, the disease remained limited to the cervix.

For comparison and as control cases the records of 27 patients treated previously by the usual routine of silver salts, douches, and urinary antiseptics were studied. In these cases duration of treatment ranged from six weeks to twelve months with an average of five months. In many, complications such as Bartholinitis, pelvic peritonitis, and salpingitis developed during the course of treatment. Many of these patients discontinued their visits to the clinic because of lack of improvement. The percentage of recurrence of symptoms and positive smears in this group was high but exact figures are not available.

The results of the complement fixation tests are of interest as shown in Table IV. This test was performed by the Illinois State Public Health Laboratory and was done in all of our cases except 6. All these patients showed positive clinical signs of gonorrhea and had

positive smears. Yet, only 16 of them had positive complement fixation tests. The remaining 23 cases were reported negative. Of the cases which were positive, 6 showed a reversal to negative when the test was repeated within one to six months after clinical cure.

TABLE IV. RESULTS OF COMPLEMENT FIXATION TESTS

RESULT OF TEST	NUMBER POSITIVE (1 TO 4X)	NUMBER NEGATIVE	POS. CASES WHICH BE- CAME NEG. AFTER CURE
No. of cases	16	23	6

So-called toxic effects occurring during administration of sulfanilamide were noted in 26 cases (57 per cent). In none of these were the manifestations severe enough to require withdrawal of the drug and no fatal or serious complications occurred in the entire series. Even the pregnant patients, one of whom received the drug about a week before term, showed no harmful effects, nor were any effects on the babies reported. The most frequent side effect noted was nausea, which varied from a mild and transitory type to a moderately severe degree, and occurred in most cases on the first day or two of administration of the drug. Vomiting on the first day or two occurred in 2 cases. Dizziness was a fairly frequent complaint and occurred either as the only symptom or associated with nausea or vomiting. One patient stated that while taking the drug she experienced "drawing pains" in both arms and legs not severe enough, however, to interfere with her housework. Another patient stated that she felt a tingling in her hands and feet; still another complained that the drug stimulated her and made her feel "jittery" and that as a result she slept poorly during the period of medication. Other effects noted included cardiac palpitation, a feeling of light-headedness, drowsiness, a tired heavy feeling, and repeated headaches.

No abnormal urinary findings or blood pressure changes were noted on routine examination in any of our cases. In a few patients blood counts and hemoglobin determinations were done before and after treatment, but no significant blood changes were noted.

Five cases of Bartholinitis occurred in this group, and all cleared up without incision. One had been incised prior to the patient's coming to us and was very tender and draining profusely when first seen. In this case, as in others, treatment consisted only of the sulfanilamide plus hot sitz baths. All five cleared up within five to ten days and each of these patients experienced relief from pain and tenderness within three days after beginning the treatment.

#### DISCUSSION

Sulfanilamide, in our experience with this small series of cases, is a very effective agent in the treatment of gonorrhea in women. It seems far more rational to treat an infection by general measures than by local application of various bactericidal drugs, and it is more

applicable to the conditions of practice than artificial fever therapy which was so highly recommended at one time.

Our cases have shown that smaller doses of sulfanilamide given in interrupted courses are a very effective method of administering the drug and avoids the danger of occurrence of severe toxic reactions.

In some of our cases a change in the smear appearance of the organism was noted after they had begun to take the drug. Many or all of the organisms were found extracellularly and the gonococci tended to be arranged in isolated pairs or groups of pairs instead of the typical tetrads and clumped diplococci formations ordinarily seen. This peculiarity of the smears was also noted by Herrold<sup>4</sup> and by Jones.<sup>27</sup>

The patients seemed to follow a definite course toward cure after administration of the drug. In most cases the woman reported a marked improvement in subjective symptoms and general well being with a diminution or disappearance of the discharge on the first weekly visit after the medication. Following this the local findings gradually cleared up from week to week. In three cases, large adnexal inflammatory masses up to baseball size could be felt gradually decreasing in size on successive weekly visits and finally disappeared entirely in about four to six weeks. The disappearance of similar masses under other forms of treatment in the same length of time is of course possible, but we feel that it is relatively rare that this occurs, and we would not expect this to happen three times in such a small series under other forms of treatment.

It should be emphasized that many of our patients had been under treatment with argyrol, silver nitrate, etc., for long periods without improvement, and yet these promptly improved and were cured with from one to three courses of sulfanilamide. One patient who had been complaining of pain and swelling in her right knee reported complete relief from the arthritis even before the genital findings had disappeared.

#### SUMMARY

1. Forty-five cases of gonorrhea in women have been treated with a sulfanilamide derivative (neoprontosil) in doses of 40 gr. daily in five-day courses. Cure was accomplished in all cases except one.

2. No serious toxic effects were observed with this dosage.

3. In the cases in which the infection was limited to the cervix and lower genital tract, no upward extension was observed under treatment.

4. Reinfection occurred 14 times in this series, but never while the patient was under active treatment, and always responded promptly to further medication.

No conclusions are justified from such a small group of cases. The results, however, are so uniform and so striking that we are greatly encouraged to continue with this method of treatment until a sufficient number of cases has been studied to confirm or deny its therapeutic value.

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## DISCUSSION ON PAPERS OF DRs. MORRIS AND BOMZE

DR. HARRY CULVER.—The concentration of sulfanilamide in milk as reported tonight corresponds very closely with that noted in urethral exudates under reasonably similar conditions. This concentration is usually somewhat above that found in the urine of the same patient.

Dr. Morris used what is generally considered as safe doses on hospitalized patients over a necessarily short period. Even then he had side reactions, such as anemia, sensory disturbances, gastrointestinal symptoms, etc. There is a tendency to prescribe enormous doses of this drug to all kinds of patients, even though it has been shown that there is an individual susceptibility to toxicity which cannot be anticipated.

Neoprontosil, the derivative used by Dr. Fall and his associates, has been found to be about 40 per cent less toxic than sulfanilamide. Its clinical behavior is similar but it is generally considered slightly less effective. I am in complete accord with their conservative dosage of 40 gr. of neoprontosil a day in young ambulatory patients. In general, especially when sulfanilamide is used, observation of the patient should be made more frequently than once a week. Untoward reactions may occur within the first forty-eight hours of administration and serious complications have been observed following the continuation of the drug under these circumstances. The dearth of serious side reactions in this study of Drs. Falls, Bomze and Fuerster is, however, striking and perhaps can be explained by the fact that neoprontosil was used instead of sulfanilamide.

A cure of 44 out of 45 patients suffering from acute or chronic gonorrheal infections, in from two to nine weeks, indicates a miraculous advance in the management of such infections. I believe, however, a more strict criterion of cure might show some recurrences. While three negative smears at three successive weekly examinations would ordinarily seem adequate, a provocative application after the use of sulfanilamide does sometimes result in the reversal to a positive smear.

Reappearance of symptoms and positive smears in 14 patients after exposure undoubtedly represents some reinfections, but we must not disregard the possibility of recurrence. Activation of subclinical gonorrhea by exposure to non-infected males is not unusual. It is clearly established that a subclinical or carrier state frequently results from the treatment of gonococcal infections with sulfanilamide.



Many reports have appeared during the last year or so on the results obtained in the treatment of gonorrhea with sulfanilamide and these vary from 90 per cent to 65 per cent of cures in all classes of cases. It is noteworthy that the more thorough the clinician, the lower will be his percentage of cures.

It has been shown that the high blood levels of sulfanilamide in either free or conjugated forms are not necessary for a satisfactory response and that the degree of response is therefore in no direct proportion to the blood level of sulfanilamide or to its concentration in the urine in genitourinary infections. Success has been noted with a blood level of 1.7 mg. per cent of sulfanilamide and failure with the concentration of 15 per cent of total sulfanilamide in the blood. In ordinary urological practice a maximum of 60 gr. a day preferably given in six 10 gr. doses both day and night for two days followed by 40 gr. a day for five to seven days would be considered adequate for one course. These medium doses given to patients under frequent observation may be either temporarily lowered or raised with benefit as indicated by the general condition of the patient.

While sulfanilamide has thus far proved itself, in general, to be the most active and efficient urinary antiseptic, it cannot be expected to do the impossible by being effective in the presence of foreign bodies such as stones or being active in the presence of any appreciable degree of urinary stasis. In the latter case, it has been observed that the urine can be kept bacteriostatic only as long as the individual is under the influence of the drug. Withdraw the drug and the original condition recurs. This drug acts best in an alkaline medium and ordinarily is tolerated better and gives a better response when taken with sodium bicarbonate.

For urinary tract infections of any type it has long been considered that diuresis produced by the ingestion of fluids has an important bearing on the clinical course of such infections. This procedure is sound and does not in any manner interfere with the curative action of sulfanilamide.

It might be of interest to state that studies of several patients with sulfanilamide fever in every instance have revealed the presence of a marked secondary anemia. Whether this anemia has anything to do with the production of fever or not, it is impossible to state but I think it is worth noting that these two conditions frequently accompany each other.

DR. PAUL C. BARTON.—Shortly after the first reports of the use of sulfanilamide appeared in the American literature the Council on Pharmacology accepted it but in doing so it was very careful to issue a number of cautions. The Council stated that it was necessary to observe carefully the effect on the blood because of the danger of sulfhemoglobinemia and methemoglobinemia. Dr. Morris has stated that the cyanosis is not related to sulfhemoglobinemia or methemoglobinemia. In spite of that fact, cyanosis indicates a rather serious condition and I am not sure it should be totally disregarded in using sulfanilamide.

Other warnings included the avoidance of magnesium sulfate, and the combination of sulfanilamide with other drugs on the basis that until more study had been made of its pharmacologic effect, and the pharmacologic effect of other drugs in combination with it, it is better to avoid such combination.

I can unofficially state that the Council will re-write its chapter on sulfanilamide in the next edition and the use of the drug in wider fields will be discussed. I do not think the Council will change its warnings.

We must be careful to limit the use of the term "sulfanilamide" to one chemical entity and not to apply it to combinations of sulfanilamide with other radicles. Neoprontosil is not the original prontosil, but both "prontosils" are compounds of sulfanilamide and azo dyes. There are literally hundreds of sulfanilamide and prontosil preparations which are available and which have been used clinically.

It might be well to consider a few of these derivatives. One is sulfanilamide-pyridine. Editorial comment in the *Journal of the American Medical Association* appeared within the last month and was in effect another warning. Let us be cautious until we know what it will do in pneumonia. Incidentally the journal pointed out that this drug is not undergoing the same rapid promotion that

sulfanilamide did, owing to the new food and drug law. It is more toxic than sulfanilamide. It may have a different therapeutic index as indicated by comparison of the physiologic dose with the toxic dose. I do not think it holds much promise.

Another derivative is acetyl-sulfanilamide which was discussed by Dr. Hae in connection with the excretion of sulfanilamide by the mammary gland. Acetyl-sulfanilamide is more toxic than sulfanilamide, and yet we find it as a form in which sulfanilamide is excreted. I think we might consider the possibility that the acetyl-sulfanilamide that is administered cannot be detoxified by a simple acetylation in the body. It may be for that reason that the preparation is more toxic.

DR. W. C. DANFORTH.—I wonder if it would not add to the value of subsequent work if blood levels were observed. It has been suggested that a concentration in the blood of 7 to 10 mg. per 100 c.c. might be accepted as a therapeutic level. I have heard that in the large medical services of New York they are using larger doses than we have been accustomed to use. On the other hand, Dr. Culver stated that the blood concentration was not a matter of great importance.

DR. V. D. LESPINASSE.—Sulfanilamide can cause fever, and the physician must determine whether any fever during the course of therapy is due to the drug or to the disease. If due to an exacerbation of the disease, the dose should be decreased; if the fever is due to the sulfanilamide, then the drug should be stopped. The fever from sulfanilamide comes on from the third to the tenth day in the course of treatment.

Sulfanilamide is used in streptococcal infections, and often ultraviolet ray is used as an adjunct. I have found that sulfanilamide makes the skin photosensitive, and when one uses the ultraviolet ray with it, the patient develops a marked erythema. I have seen this condition in two cases: one with an erysipelas on the forehead, and the other with a streptococcal pneumonia; both of these patients have been treated locally with the ultraviolet lamp.

DR. BROMZE (closing).—In reply to Dr. Danforth's question about blood levels of the drug, it was found by the Mayo group, who did most of the work with neoprontosil, that even with large doses no higher levels than 3 mg. per 100 c.c. were reached. We did not feel that it would be of value to repeat that phase of the work.

DR. HESSELTINE (closing).—Two problems were mentioned tonight, namely, gonorrheal infection and puerperal infection. They are entirely different in their severity. Naturally in puerperal infection which has a high mortality we are justified in taking a chance with the drug only when its use is properly indicated. On the other hand, gonorrheal infection though it may cause damage does not produce nearly as much mortality, and hence greater caution is required in the use of the drug.

It has been our policy not to treat a patient with sulfanilamide until we know what the offending organisms are and then apply the sulfanilamide therapy only in patients where the bacterial invaders are supposedly susceptible to the drug. We are still doing experimental work. We have not found it of any value in the treatment of puerperal infection other than that due to *Streptococcus hemolyticus*; we are using it in gonorrheal infection.

We have changed our policy about cure in gonorrheal infection. Formerly we relied entirely upon the smear. We have found with the administration of sulfanilamide that this has not been reliable. In one patient the culture was positive for fifty-one days after the smears became negative, and remained negative.

DR. MORRIS (closing).—We did not make blood concentration determinations at the Cook County Hospital because they were not being done when we started the work.

We found that in some cases fever occurred from the fifth to the ninth day after beginning the drug. It is difficult to say whether it is due to the infection or to the drug. Usually we find the temperature dropping by the fifth or sixth day and if it rises we think it may be due to the sulfanilamide.

In regard to anemia, one of our patients had taken only 60 or 70 gr. when she became very anemic. Our patients are closely watched for this complication. Colebrook, of course, recommended sulfanilamide only in hemolytic streptococcal infections. It is now used for practically everything and we are endeavoring to evaluate its effectiveness in puerperal infections due to other organisms.

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## ABORTIONS IN RELATION TO VIABLE BIRTHS IN 10,609 PREGNANCIES\*

### A STUDY BASED ON 4,500 CLINIC HISTORIES

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MANY authors have investigated the course and termination of pregnancies with particular regard to interruption before viability. One needs only to glance at the greatly varying estimates and dissimilar criteria for these studies to realize that we are still far from knowing what percentage of conceptions reach viability or will be wasted, either spontaneously or willfully. Not only are we uncertain as to the number and types of pregnancy wastage; but the causes which operate in bringing about spontaneous or induced abortions are to a great extent unknown.

### SOURCE AND CHARACTER OF MATERIAL

The present study is an attempt to throw further light on the above questions by examining statistically the clinical histories of a large number of women. The results represent careful researches into 4,500 consecutive histories taken between the years 1930 and 1938, at New York University College Clinic, Department of Obstetrics and Gynecology. These histories were obtained originally with no regard for special data necessary for the present investigation; hence, some of the important related facts are not always available. The patients were interviewed by several examiners, but always with a uniform technique supervised by the senior author.

The clinic is an organic part of a general dispensary located in New York City. The patients' incomes do not exceed \$900 per annum if they are single, or \$1,400 if married, maximums determined by the Joint Conference of New York Hospital Conference and County Medical Societies. Because of these restrictions, the economic standardization of the group under consideration was uniform.

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\*We are grateful to Mr. William S. Goldfarb, M.S., for preparing the graphs and tables which appear in this article.

Further particulars as to economic standardization were sought, on the basis of home rental. Figures, however, were only available in about one-half of the charts. There was also a large diversity of neighborhoods and number in each family sharing an apartment. It was therefore decided to abandon this procedure as too confusing.

Although there were small nationality groups, within the population sample here studied, who continue to speak their own language, live in a circumscribed neighborhood, cultivate each other's company and maintain their old world habits, it is conceivably true that their reactions to the questions under consideration would be uniform, and yet different from the majority of the patients. There were, however, so many nationalities and races represented in these small groups, that any information gained from their individual study would be inconclusive and misleading. It should nevertheless be stressed that there were a negligibly small number of recent immigrants among the patients.

The only racial group considered separately was that of the negro, which comprised 6.3 per cent of the total. The incidence of pregnancies and spontaneous and induced abortion was identical with that obtained for the entire group, so it was decided to include them without reservation.

Lacking complete figures on which to base a differential fertility and abortion rate, according to the occupations of the patients' husbands, or their own employment, it was estimated, by means of samplings, that two-thirds of the patients were wives of skilled or semi-skilled laborers and small business men. The remainder were preponderantly working women doing clerical or sales work, with a small scattering of waitresses and domestic workers.

As for the education of the patients, most of them had at least some high school training, with less than one-third completing secondary school.

*Definition of Terms.*—When pregnancy is carried for twenty-six weeks or more, it is here considered a viable birth. All premature deliveries and stillbirths are included.

For lack of more exact terminology, where the exciting cause of abortions is vague, unknown, or not directly due to willful interference, they are classified as spontaneous.

Abortions which are caused by instrumentation or toxic medications of hormonal or oxytocic nature are referred to as induced. Included in the medicated group are only those in which pregnancy was without a doubt proved.

*Major Findings.*—According to the above definitions, 3,216 patients of the entire group of 4,500 had 7,712 viable births, 1,681 spontaneous and 1,216 induced abortions, a total of 10,609 conceptions.

Stated in percentages, 72.7 per cent of all pregnancies reached viability; 15.8 per cent were wasted spontaneously and 11.5 per cent by induction.

The average number of viable births among the group of 3,216 parous patients was 2.4 per cent each; 1,497 of these women, or 46.5 per cent, had one or more pregnancies terminated by abortion. Of the 10,609 conceptions, 2,897, or 27.3 per cent, were terminated by abortions. Of the patients (1,497) who had abortions, the average number of abortions per patient was 1.9.

One thousand two hundred and eighty-four patients, or 28.5 per cent, of the total number of women studied, had either successfully prevented conception or were unable to become pregnant. Only 155, or 12 per cent, of these patients stated that they did not use contraceptive methods of any kind.

### COLLATERAL INFLUENCES

Some of the collateral influences which bear upon pregnancy and its termination are: (1) Economic; (2) social point of view, as shaped by state and church; (3) age; and (4) legitimacy.

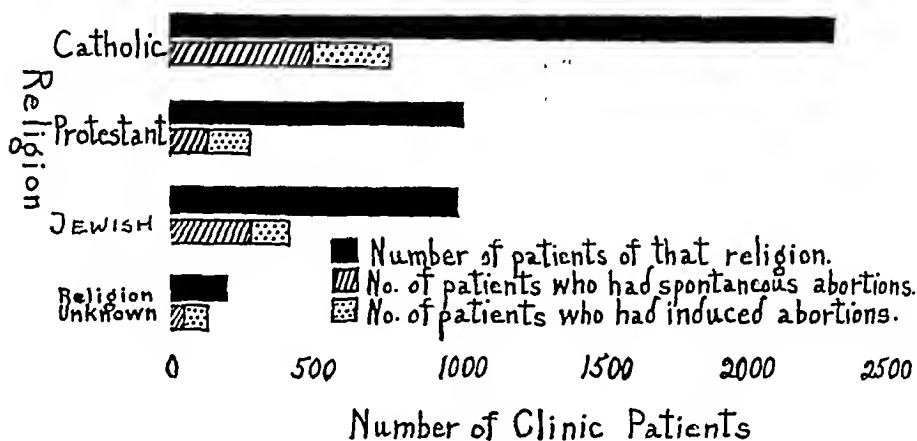


Fig. 1.—Incidence of abortion in 4,500 consecutive clinic patients, with religious affiliation. Total number who were never pregnant, 1,284 (married, 972; single, 312). Total number who had abortions, 1,497 (spontaneous, 991; induced, 506). Number of married patients who had abortions, 1,464; single patients, 33.

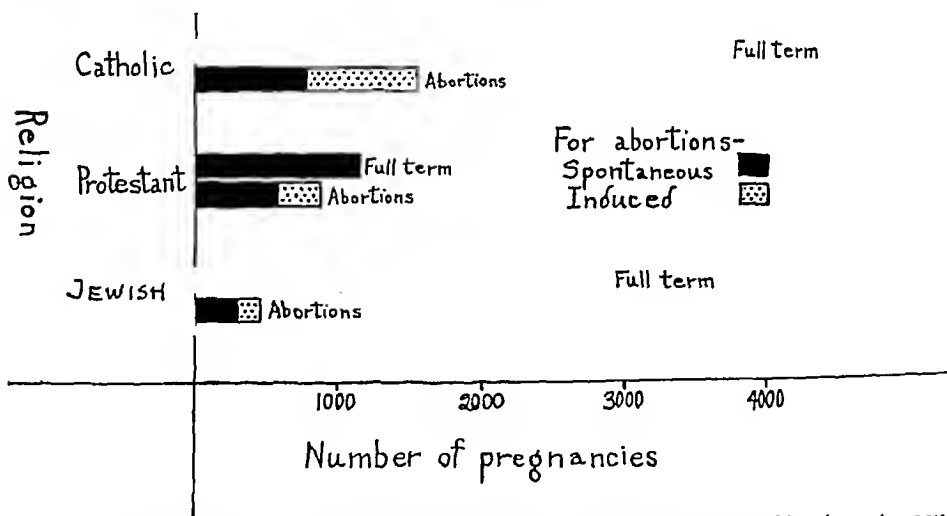


Fig. 2.—Outcome of 10,609 pregnancies: Viable, 7,712; abortions, 2,897 (spontaneous 1,681; induced, 1,216). Showing distributions among religious groups.

In the following pages a breakdown, under these headings, of the information in the clinic charts, will be given by means of tables, graphs and brief discussion.

**Economics.**—As previously stated, this is an economically homogeneous group. If light is to be thrown on the influence of family income upon the subject here under consideration, a similar study of another standardized economic group is necessary as a basis for comparison.

**State and Church.**—The state and church take very positive interest in the family and pregnancy. That the former failed to control by stringent legislation the practices of contraception and willful abortion need not be gone into at this time. Since the termination of pregnancy to a large extent depends upon the will of the patient,

it seemed to us important to investigate how much influence religious beliefs exert upon conception and abortion. It was decided that the results of the investigation be separately expressed for the three main church groups, to ascertain if there is any variation, due to religion, within the same economic class.

Fig. 1 shows that approximately half of the group studied were Catholics. The remainder were divided almost equally between Protestants and Jews, leaving a small and unimportant group in which the religion was not given.

This graph illustrates the fact that both spontaneous and induced abortions occur in all groups.

Theoretically there should be no appreciable difference in the frequency of spontaneous abortion among the various religious groups. Yet approximately twice as many spontaneous abortions are recorded for Jewish as for Protestant women. The rate for the Catholic group was only slightly lower than that for the Jewish.

One would have expected some real differences when induced abortions were studied. However, these proved to be almost negligible. Approximately 12 per cent of Catholic women, 14 per cent of Protestant and 13 per cent of Jewish women had had induced abortions.

More interesting figures are shown in Fig. 2, which shows that 51 per cent of Catholic women had an average of less than two children each. Though the percentage of those who had had induced abortions was somewhat smaller than in the other groups, the number of women who had had repeated abortions was high enough to make the ratio between induced and spontaneous abortion 1 to 1.

The Protestant women had an average of approximately one viable birth each, and the ratio between viable birth and abortion was 1.3 to 1. The relationship between spontaneous and induced abortions was about 2 to 1.

The Jewish women were the most fertile. They averaged almost three children each, and although a large percentage of the Jewish women, as seen in this graph, had induced abortions, the total number of them was comparatively low. The relation between spontaneous and induced abortion was similar to the Protestant group: 2 to 1.

*Age, Marriage and Termination of Pregnancy.*—The 4,500 consecutive patients, or the population group here represented, had an average age of 34 years. The women who had children were older, an average of 35.7. The ones who had never been pregnant were younger—30.1 years. The average age at which marriage occurred was calculated for the parous and nonparous groups separately. For the nonparous group it was found to be 22.5 years. Considering the parous group: at the age of 24, 68.2 per cent of the Catholic women, 69.2 per cent of the Protestant women, and 70.7 per cent of the Jewish women were married. The mean ages at which these three groups married were respectively 22.3, 22.5, and 22.4, an average for the whole group of 22.45 years.

The average age at the first clinic visit of parous patients was: Catholic, 35.8 years; Protestant, 32.3 years; Jewish, 38.7 years. Detailed age distribution is shown in Table I.

TABLE I. PATIENTS, BY AGES, AT TIME OF FIRST CLINIC VISIT

AGE	CATHOLIC	PROTESTANT	JEWISH	PATIENTS NEVER PREGNANT
Up to 24	293	170	69	492
25-29	233	138	71	260
30-34	289	105	105	204
35-39	347	66	117	112
40-44	234	71	101	84
45-49	179	43	98	31
50-54	94	6	29	54
55-59	22	20	33	35
60-64	7	8	22	11
65-69	10	4	5	1
70-74	24	0	0	0
Totals	1732	631	650	1284

Interesting figures were obtained by calculating the number of viable births occurring to women of the various church groups up to and including the arbitrary age of 30 years. These figures were arrived at by dividing the total number of viable births up to the age of 31 by the total number of patients for the several groups. Thus it was found that the Catholics had 1.36, the Protestants 0.82, and the Jewish 2.26 children.

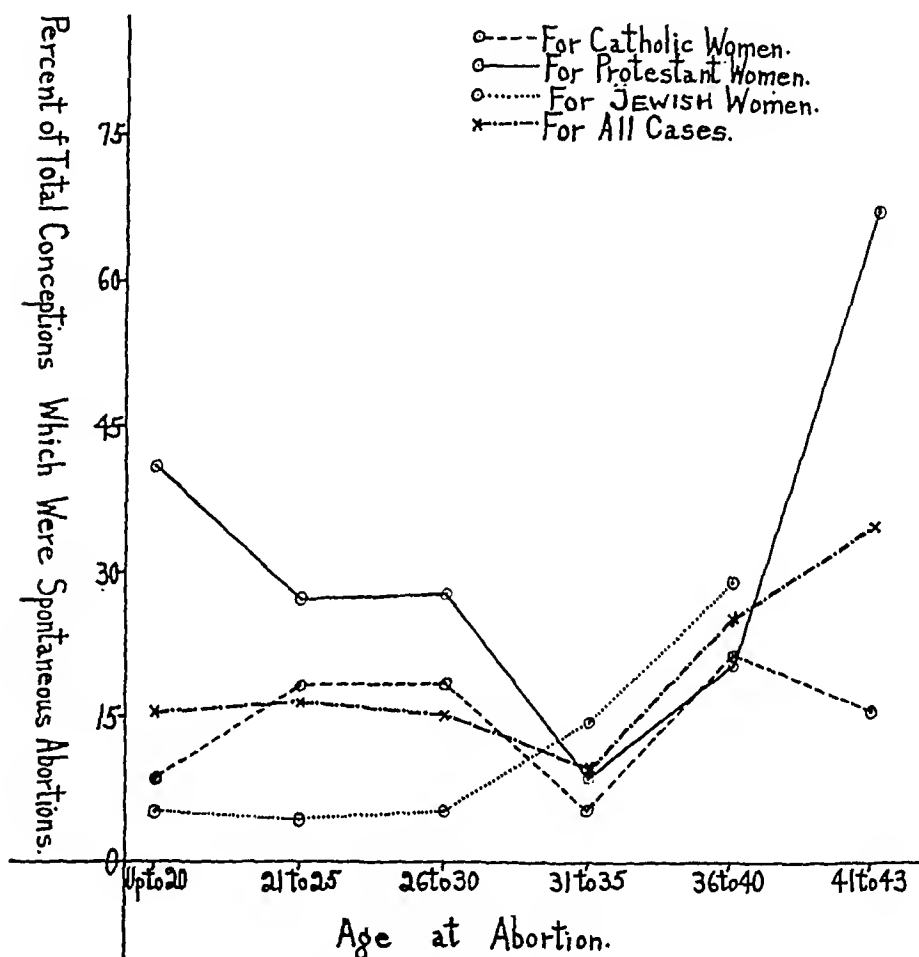


Fig. 3.—Relation of spontaneous abortion to age.

All cases considered, the mean of the pregnancies carried to viability occurred at an average of four years following marriage. This happened regardless of at what age the marriage took place. Table II shows that the largest number of abortions, both spontaneous and induced, occurred around the age of 23 with a very gradual diminution from then on.

The results separately plotted for the various church groups (see Fig. 3) show that there was a fairly constant level of the spontaneous abortions from the early childbearing period up to 26 years of age. From then on there was a general lower-

TABLE II. RELATION OF ALL ABORTIONS TO AGE

AGE AT ABORTION	UP TO 20	21 TO 25	26 TO 30	31 TO 35	36 TO 40	41 TO 45
Spontaneous abortions	263	626	445	130	161	56
Induced abortions	117	406	345	173	91	84

ing for a period of ten years, and a sharp rise thereafter. It might be stated that between the ages of 30 and 35 fewer conceptions ended in spontaneous abortion than at any other age. The relatively low spontaneous abortion rate for the Catholic women above the age of 40 is due to the fact that at that age the number of induced abortions in this group, as will be shown in the next graph, was approximately 80 per cent.

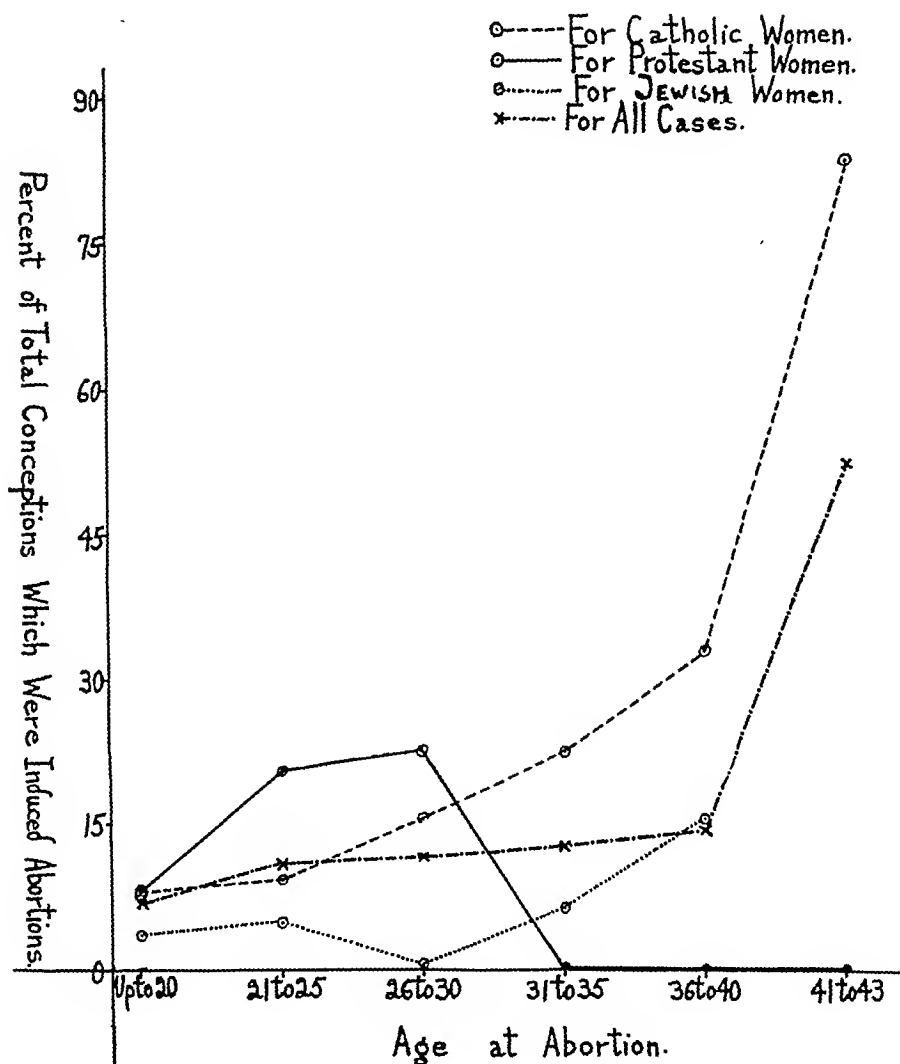


Fig. 4.—Showing relation of induced abortions to age.

Fig. 4 shows results in a companion study, demonstrating the relationship between the ages of the patients and the induced abortions. With advancing age the percentage of induced abortions rises markedly, in both the Catholic and Jewish groups. The Protestant women have no induced abortions recorded in our charts after the age of 35. The probable explanation is that the fertility rate is so low in this group that at this age they are willing to carry any pregnancy to its natural termination.

The distribution of conceptions according to the number of years married is shown in Table III. In Table IV the occurrence of abortions, spontaneous and induced, respectively, is expressed in percentages. There is a slight general rise in the spontaneous abortion rate in relation to the years married. The factor that



TABLE III. DISTRIBUTION OF CONCEPTIONS BY YEARS MARRIED

	NUMBER OF YEARS MARRIED				
	0-4	5-9	10-14	15-19	20-23
Catholic	3094	1465	442	70	91
Protestant	1481	271	193	64	22
Jewish	1458	1067	510	288	29
Totals	6033	2803	1145	422	142

TABLE IV. RELATION OF NUMBER OF YEARS MARRIED, TO ABORTIONS

		NUMBER OF YEARS MARRIED				
		0-4	5-9	10-14	15-19	20-23
Percentage of conceptions ending in spontaneous abortion	Catholic	15.3	17.5	6.8	20.0	17.6
	Protestant	31.0	18.5	30.1	34.4	0
	Jewish	4.5	4.0	25.3	19.1	31.0
	For all cases	16.5	12.5	19.0	21.6	17.6
Percentage of conceptions ending in induced abortion	Catholic	7.7	18.4	29.2	62.9	82.4
	Protestant	16.3	17.7	0	0	0
	Jewish	4.4	1.1	7.5	12.5	69.0
	For all cases	9.0	11.7	14.6	19.0	66.9

patients marry at various ages interferes with any significant deduction from these data. Otherwise expressed, the age of the patient might as tellingly affect the spontaneous abortion rate as does marriage and consequent pelvic trauma.

There is a steady rise in the induced abortion rate with the number of years of marriage. The conclusions are similar to those arrived at when the relation of age to induced abortion was studied.

It is striking that the desire for interruption of gestation in the older women was on the whole so prevalent. It might, however, be reasonably assumed that some of the induced abortions in these patients would have ended, if allowed to continue, in spontaneous abortions. This assumption would be particularly reasonable in those abortions which were induced by medications.

*Legitimacy.*—The question of how the legal status of marriage affected these results was next examined.

Fear of illegitimacy is said to be an important cause of induced abortions. It was found, however, that at the time of interruption there were only 33 women, among the 1,497 giving a history of induced abortion, who were not married, either at the time of abortion or of interview, a number sufficiently small so that it can be dispensed with as an unimportant force in this particular study.

*Gestation-Month of All Abortions, and Method of Induction.*—The time of gestation at which abortion took place is represented in Table V. The largest number of spontaneous abortions occurred in the third month. The largest number of induced abortions were performed in the second month of gestation.

TABLE V. GESTATION-MONTH OF ALL ABORTIONS\*

	GESTATION-MONTH			
	FIRST	SECOND	THIRD	FOURTH AND LATER
Spontaneous abortions	41	294	357	239
Induced abortions	76	152	69	85

\*The gestation-month of 744 spontaneous abortions and 840 induced abortions was not specified.

The method of induction was predominantly instrumental and 984 times a doctor was behind the instrument. Self-induction was admitted only by 103 patients. At least twelve of these were instrumental. Midwives were responsible for the abortions on only 33 women.

TABLE VI. MORBIDITY

IMMEDIATE				REMOTE				
	CONFINED TO BED FOR FEVER AND BLEEDING	ACUTE PELVIC IN- FLAMMATION	CERVICITIS		DISPLACE- MENTS (BACKACHE)	ABDOMINAL PAIN NOT DUE TO INFECTION	ABNORMAL MENSTRUA- TION	STERILITY
			TOTAL NUMBER	WITH LEUCORRHEA				
1216 induced abortions	151 (12.4%)	29 (2.46%)	212 (17.5%)	96 (7.9%)	124 (10.0%)	111 (9.0%)	68 (5.5%)	19 (1.5 %)
1681 spontaneous abortions	98 (5.8%)	41 (2.4 %)	191 (11.3%)	133 (8.0%)	150 (8.9%)	190 (11.3%)	105 (6.0%)	6 (0.35%)
7712 viable pregnancies	-	38 (0.5 %)	241 (3.0%)	188 (2.4%)	121 (1.5%)	317 (4.0%)	198 (2.5%)	-

*Morbidity.*—A morbidity tabulation is attempted in Table VI. The immediate and remote after-effects are listed separately. Under immediate is classed the presence of fever, bleeding or pain requiring confinement in bed for over forty-eight hours. Among the remote consequences it was not attempted to list every possible instance, but to limit the figures to those in which, after careful investigation of the physical findings and history, we were convinced that the symptoms and diagnoses were definitely related to a here recorded birth or abortion.

#### SUMMARY AND CONCLUSIONS

1. The histories of 4,500 consecutive patients attending a gynecology clinic were the basis for the foregoing study.

2. The patients belonged to groups economically and culturally similar, but socially and religiously heterogeneous.

3. The terminations of 10,609 pregnancies were analyzed, showing that: (a) 72.7 per cent of all pregnancies were carried to viability; (b) 27.3 per cent of the pregnancies ending in abortion: (1) 15.8 per cent, spontaneous, and (2) 11.5 per cent induced.

4. Of the 4,500 patients, (a) 71.5 per cent were parous; (b) of the remaining 28.5 per cent, or nonparous, 12 per cent used no contraceptive methods.

5. Of the parous group, (a) the average number of viable births per patient was 2.4; (b) 46.5 per cent had one or more pregnancies terminated by abortion; (c) the average number of abortions per patient among those with records of interrupted pregnancies was 1.9.

6. Out of the total of 4,500 patients, approximately half were Catholics, the remainder divided equally between Protestants and Jews.

7. The largest number of viable births were found among Jewish women, the smallest among the Protestant.

8. The average age when marriage took place in both parous and nonparous women, regardless of religion, was 22.45 years.

9. The mean of all viable pregnancies occurred in the fourth year of marriage.

10. Spontaneous abortion rate was highest in the Jewish group, lowest in the Protestant.

11. Induced abortion rate was approximately the same in all religious groups, an average of 12.5 per cent.

12. Both spontaneous and induced abortion rate increased with advancing age and the length of time a woman was married.

13. The incidence of pregnancies and abortions was the same in negroes and Caucasians.

14. Induced abortions were performed in the majority of cases by physicians.

15. Morbidity statistics are presented.

## MALARIA IN RELATION TO OBSTETRICS AND GYNECOLOGY

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**M**ALARIA is both a social and a medical problem in the island of Puerto Rico, and thus constitutes also more or less of an obstetric and gynecologic problem. Being generally endemic throughout the island, it occasionally breaks out in true epidemics, in spite of the great and laudable efforts of the local Department of Health operating in conjunction with the Rockefeller Foundation in their well planned campaign for the total eradication of the disease.

A study of the relations of this disease to obstetrics and gynecology should prove interesting and enlightening to those specializing in this line of work in the island, and possibly also to obstetricians and gynecologists practicing in nonmalarial districts, or in regions where malaria has a very low incidence.

The above considerations and the fact that no report on this topic appears in our regional medical literature, has tempted me to make a survey of the literature and to summarize my personal experience in this field. The usual sources of information have afforded rather meager knowledge; the majority of textbooks and treatises on gynecology and obstetrics are very poor in their information, and a perusal of the available original medical literature shows that even this body of material, so rich in other phases of medical observation and research, is also rather weak in the discussion of this problem.

The influence that the infectious diseases produce in the normal and pathologic processes of the genital organs is a well-known and established fact. With this generally accepted dictum in mind it would be impossible to hope that the numerous and serious disturbances that malaria produces in the human organism would leave undamaged the organs of generation which are so sensitive to the systemic reactions.

The pathogenesis of malaria in relation to the female reproductive organs remains at present not well understood. In some of the cases where the process alters the glandulogerminal activity, the pathologic damage consists in the nidation of the pathogenic agent directly in the ovary with the subsequent production of a specific oophoritis, but in other instances it is the bacterial toxins or the toxins from deranged metabolic processes in the diseased organism, which act, through the agency of local nutritive disturbances or prolonged elevations of temperature.

The scientific research and evaluation of the exact and definite components of this mechanism, the true detection of the invisible originators

of the pathology present in each and every case, constitutes at present a very difficult problem because of the lack of experimental evidence.

There is no doubt that with the rapid advances in the experimental sciences and the interest that the study of malaria has recently created in the various institutions of tropical medicine, much needed light on the darkness of this question will soon come to clarify the intricacies of this problem, thus increasing its practical and theoretical importance.

Without doubt, of all the infectious diseases malaria is the one which produces the least anatomic disturbance in the female genitalia. Nevertheless, the observation, study, and research on this topic have shown that it produces sufficient functional and pathologic changes to warrant their discussion for the benefit of the general practitioner and also for the specialist not well acquainted with malarial infections.

Of these pathologic disturbances there is one which should receive noteworthy mention because it is an unusual condition which is generally misinterpreted. I refer to gangrene of the external genitalia. This condition is rare but has been observed by various students of this subject. In some cases it is found in very small patches, especially around the labia, but in others it spreads into large and alarming extensions.

It is logical to think, though it is not as yet a proved fact, that malaria, during infancy and early childhood because of the frequent and repeated relapses during this period, is liable to produce in some cases serious retardations and suspensions in the development of the genital organs.

It is well known, and this has been proved by pathologic evidence, that the infectious oophoritis is responsible for many hypoplasias and atrophies of the genitals. These constitute, without doubt, some of the cases of atrophies and hypoplasias which are found, with great surprise, during the course of gynecologic examinations, in women who are otherwise well developed and who present no evidences of endocrine disturbances or hereditary traits.

I have repeatedly observed a noticeable increase in the vaginal discharge of women suffering from chronic adnexal disease during the course of malarial attacks. I have also observed that this increase in the vaginal exudate has not the beneficial effect in the pathologic findings that we often encounter after the artificial fever produced during a course of lacterotherapy. Whether this increase in the vaginal discharge is merely due to congestion and hyperemia of the pelvic organs or to some special action of this protozoan infection, I am not prepared to state at the present moment.

The functional disturbances of the ovaries are quite frequent. They are manifested by meno- and metrorrhagia if the infection is of short duration, and by amenorrhea and sterility if the process is chronic and of long standing.

When the disease appears in the premenstrual period, the menses generally start before the expected time. Whether this condition is due to the death of the ovum or to hyperemia of the pelvic organs is a question not yet definitely settled. At times the menses not only appear before the expected period, but the flow is also alarmingly

increased, especially in cases where the infection develops at the same time as the apparition of the menstruum. If the infectious process starts immediately after the end of the flow, it is not at all rare to observe a reappearance of the menses, though in some cases just the opposite occurs: a stoppage of the ovarian activity with subsequent production of amenorrhea. As a general rule, the menstrual cycle is definitely re-established in the course of time, except in those rare cases in which the ovaries have suffered irreparable damage, with development of a subsequent sterility as in the cases observed by Schaeffer.<sup>1</sup>

The relation of malaria to sterility is by no means a recent observation, nor is Schaeffer alone in considering it to be an established fact. Laffont<sup>2</sup> states that it was known in ancient times and that Hippocrates "knew of the scarce capacity of the malaric for conception" and Novak<sup>4</sup> also states that sterility is widely spread in regions infected with malaria.

Although these observations carry a certain authority because of the intellectual caliber of the observers and although I personally believe that no definite statement can be made until further investigations definitely settle this point, I must confess that our experience in Puerto Rico, which is an intensely malarial region, does not correspond at all to the observations of Laffont, Schaeffer, and Novak.

We have in our island a population of about 500 persons per square mile (3,400 square miles, 1,700,000 population) and a malarial incidence of 35 to 55 per cent (Earle) with no reported case of sterility which could be traced to malaria as the causative factor. Furthermore, a consideration of the above figures will convince any one, without more detailed statistics, that our fertility rate has not been appreciably weakened by the ever present endemic of malaria in the island.

Megaw's<sup>3</sup> statement that "During an epidemic of malaria there is usually a heavy fall in the live birth rate as well as an increase in the infant mortality" is based without doubt on the malarial production of abortion, premature birth and still birth. According to Goch<sup>5</sup> malaria interrupts pregnancy in 41.3 per cent of the cases. This complication is more frequent, the more advanced the gravid state of the patient. Abortion is very rarely seen during the malarial attack, it being more frequent during the intervals between the attacks, a fact which seems to indicate that the fever per se is not the principal and determining factor in the production of the interruption.

Around this interesting topic of the definite determination of the factor or factors responsible for the interruption of pregnancy, there is an extensive and rich bibliography consisting of investigations, observations and discussions, so alluring and enlightening, that we have deemed it necessary to enumerate some of the most important, so as to give a clear idea of this phase of the problem.

Runge<sup>6</sup> believes that although the fever is not the only cause of the intrauterine death of the fetus, it constitutes nevertheless one of its most important factors. To prove his thesis, Runge has demonstrated, through animal experimentation, that short and strong thermal stimulations of the uteri of rabbits produce tetanic contractions of this organ.

He also demonstrated that the fetuses of rabbits kept in an incubator at 41.5° C. (106.7° F.) died in utero in a very short time.

On the other hand, Seitz<sup>7</sup> states that the fever plays only a secondary and unimportant part, because often the pregnancy continues undisturbed despite high and prolonged elevations of temperature. This statement reminds me of a case attended at our Municipal Hospital six years ago. The patient was a multipara v, eight months pregnant, affected by *Plasmodium falciparum*, who sustained a continuous fever fluctuating between 39° and 41° C., for a period of ten days, without interruption of pregnancy or apparent injury to the vital capacity of the fetus. One month later she was normally delivered of a living, 7-pound female baby.

According to Seitz, the principal etiological factor lies in the circulating bacterial toxins which together with the other products of albumin disintegration excite the uterus to contractions. Thus according to his theory, the fever and the uterine contractions are nothing but the effect of the same identical cause: the bacterial toxins.

Novak also believes that the responsible factor lies in the specific substances produced by the plasmodium or else manufactured in the organism under the influence of the disease.

Lauros<sup>8</sup> places the blame on the occurrence of infarcts and inflammatory conditions of the placenta together with a certain peculiar and abnormal friability of the uteroplacental vessels, but these or similar pathologic changes are so frequent in processes which are not malarial in origin that the specific value of these findings is of doubtful importance.

It is hard to blame the cachexia because clinical experience has demonstrated that even the most excessive states of anemia and hyponutrition do not impede the continuation of gestation. The passage of the plasmodium from the mother to the fetus has also been suggested as an etiologic factor, but the occurrence of this transmission is so rare that it could not serve as an explanation in every case. Neither could the blame be charged to the administration of quinine, because clinical experience has taught us that untreated patients abort with greater frequency than those which receive quinine therapy.

In all probability this complication is due to a combination of one or more of the factors enumerated above. Since this problem remains as yet unsolved, the exact determination of the role played by each one of them constitutes at present an important field of research.

According to Perkins,<sup>9</sup> Deeks "believes that eclampsia is more common in malarial districts." Laffont also believes that gravid women, affected by malaria, frequently develop eclampsia. These observations run true to our experience in the Maternity Service of our Municipal Hospital. They also correspond in some way with the newer theory of the causation of eclampsia, so well exposed by Goodall<sup>10</sup> who states that eclampsia is a nervous explosion more frequently found in the young, temperamental patients whose nervous system is very sensitive and unstable, not strong enough to resist rapid and intense stimulation. The increased incidence of the eclamptic episode in the gravid women

suffering from malaria should also make us think of the renal disturbances, so frequent in the course of this disease, as a possible etiologic factor.

Malaria also affects parturition. Although labor generally evolves normally, frequently a marked uterine inertia is present which prolongs considerably the first stage. I sincerely believe that many of our secondary inertias, so frequent in this region, are without doubt malarial in origin. These cases need close observation during the immediate post-partum period, because the atonia present during the course of labor is often responsible for serious post-partum hemorrhages. Some authors state that when labor starts during the febrile period, the pyrexia ceases immediately, to reappear after parturition is completed. I have observed this phenomenon only once. Involution is slow, torpid and retarded, constituting occasionally another factor in the causation of post-partum bleeding. During the puerperium, malarial relapses are common. Primary infection is not unusual. The general lowering of resistance, obstetric shock, loss of blood and energy are generally considered probable causes of the frequency of these relapses. The presence of malarial infection during the puerperium often results in a serious diagnostic problem, because the fever curves may be atypical and the plasmodium not detected in the examination of the blood. As a rule the history of previous attacks, their periodicity, the lack of visible pyrogenic modifications at the genitalia, the enlargement of the spleen, a leucopenic blood count, the demonstration of the plasmodium in the erythrocytes or the favorable response to the clinical therapeutics instituted will easily clarify the obscurity of the condition.

A point which merits some consideration in the study of the relations of malaria to obstetrics and gynecology is the so-called special immunity which pregnancy has been supposed to render toward malaria. Although this theory has been denied by the majority of modern writers on this topic and although I see very little scientific basis on which the theory could be defended, I wish to report that in a detailed study made for this particular purpose of the last 300 cases in my private service at the Clinic of Dr. Pila, we found only 22 cases of malaria, and 12 of them were relapses which occurred during the puerperium.

We realize that the observation and study of such a small number of cases gives no authority to speculate on this matter, especially so when well-reputed observers as Novak and Perkins flatly deny the probability of the existence of malarial immunity in pregnancy. I must add that this group of patients belong to our upper classes, whose general health is excellent, who are surrounded by splendid sanitary conditions, and who receive strict prenatal care from the very start of gestation.

These factors undoubtedly increase their individual resistance to the disease, and in all probability play an important role in lowering the incidence. But in spite of these considerations I feel that these findings are remarkable and striking and that this question yet unsettled should serve as a splendid point for further research work.



Such an authority on the question of malarial immunity as Taliaferro<sup>11</sup> states that he knows of no specific work on the relation of pregnancy to malarial immunity, but he believes from experience in his research in other lines of work, for example, in his studies on the resistance of rats to *Trypanosoma lewisi*, that this immunity, if present, might break during the latter months of gestation.

The babies born of malarial mothers show a greater mortality than those born of patients free of the plasmodium. They are generally underdeveloped, puny, and often premature. Goth states that they generally weight 339 gm. less than those born of normal mothers. Babies born of malarial mothers frequently develop malaria ten to twelve days after birth. Whether this is due to an intrauterine infection or a post-partum contact is not as yet definitely settled. Novak assures us that the placental filter is impermeable to the malarial plasmodium, but it is also well known that this filter is not always capable of resisting the entrance of pathogenic bacteria to the fetus. A great deal of experimental work has recently been performed around this question and summarizing the most important findings it appears that the placenta is impermeable to the inanimate corpuscular elements, to all non-pathogenic bacteria, but that it is also liable to invasion from those bacteria which are capable of altering the placental tissue proper.

Although this paper has been prepared with the sole idea of discussing the relations of malarial infections to the female genitalia, without the intention of entering extensively into the field of its treatment, there are certain aspects of these relations which have such an intimate contact with the therapy of the disease that we have been compelled by the force of these circumstances to consider briefly this most interesting field.

The first question to be considered is if malarial mothers should nurse their babies. This of course is a question that cannot be answered by a general rule. Each case needs for its proper and adequate solution, special study of all the factors involved. But we do know some facts and with this knowledge we are now better prepared to face and solve the majority of these problems. We know that quinine therapy does not alter the secretory function of the mammary gland and that it passes into the mother's milk in such small and inappreciable quantities that it does no harm to the babies. In our island the general belief is that quinine dries the maternal secretion of milk. I believe this false idea has been created because of the fact that quinine is generally administered here with camphor in oil, which according to Mc Neile<sup>12</sup> and Klein<sup>13</sup> produces a rapid suppression of milk secretion.

Another point which merits elucidation is the use of quinine in the presence of pregnancy. Quinine is not contraindicated in the treatment of malaria in the presence of gestation. On the other hand, great danger may result in the injudicious avoidance of the drug. The reputation that quinine has of producing uterine contractions is greatly exaggerated as has been proved by the recent experimental work of Aeton.<sup>14</sup> Williams<sup>15</sup> states that in the presence of malaria the oxytocic

properties of quinine really do not exist. More recently another problem has arisen on the question of quinine therapy during pregnancy. According to the work of West<sup>16</sup> experimental and clinical evidences show that quinine given in massive doses during the gravid state produce fetal hearing defects (degeneration in the auditory nerve, spiral ganglion and peripheral neuron).

In closing, I wish to state that it is my experience that in malarial districts where relapses are so frequent during the puerperium the judicious use of small doses of quinine immediately following labor is very beneficial, because it not only prevents the probable occurrence of the relapse, but also helps a great deal in the involutional process of the genitalia.

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## STREPTOCOCCUS VIRIDANS ENDOCARDITIS IN PREGNANCY

### WITH THREE CASE REPORTS

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SINCE the discovery of the *Streptococcus viridans* by Schottmüller in 1909, the organism has been isolated in 15 reported cases of sub-acute bacterial endocarditis during pregnancy. Among the twelve authors reporting such cases, opinion has been divided as to the management of the pregnancy, and in many instances the diagnosis has been confused with pyelonephritis or puerperal sepsis. For these reasons it would seem worth while to present three additional case reports and to review the subject from an obstetric standpoint.

Prior to the time that Osler and Horder described the clinical aspects of this disease in 1910, there was much confusion in the terminology of endocarditis. Acute endocarditis was thought to be quite common in pregnancy, and as early as 1856 Virchow described such a case and discussed the relationship between puerperal sepsis and "vegetative" endocarditis. Inasmuch as puerperal sepsis was rampant at that time, many of the cases of bacterial endocarditis arising during the puerperium were undoubtedly due to the hemolytic streptococcus. An ex-

CASE 3.—R. A., aged 22 years, para ii, gravida ii. Menses: Regular twenty-eight-day cycle, last period 10 days ago. Complaint: Lencorrhœal discharge. Physical examination negative, excepting endocervicitis.

Fig. 5, *a* illustrates that at times the electrical recording, as secured by present methods, manifests a striking parallelism with the pneumatic tracing. At times the two tracings are actually superimposed! That this can happen in such detail is remarkable, because the two systems are so different in operation. Without doubt, artifacts can be ruled out: no mechanical vibration such as jumping or stamping on the floor can cause any parallelism. (The floor, in fact, is approximately vibration-proof; for it is constructed of double thickness and strength to support safety-deposit vaults.)

Probably it is fitting to call Fig. 5, *a* a "tonus tracing"; for the picture taken very soon thereafter, using Amplifier 2 for higher frequencies only, reveals this character clearly. (Obviously, parallel tracings like those in Fig. 5, *a* could not be secured if only higher frequencies are recorded as in Fig. 5, *b*).



Fig. 4.—*a*. (Patient S. H.) Tonus in the human uterus, recorded electrically (lower tracing). One electrode in corpus, the other in cervix tissue (Type B, electroutero-gram). The pneumatic record (above) fails to show tonus clearly, for the tracing is almost a straight line, broken only by slight, concave pulse marks. 3.5 mm. = 1 microvolt. (Higher frequency record, made with Amplifier 2.) *b*, Control test. Conditions same as for Fig. 4, *a*, except that a key closes a circuit across the input terminals of the amplifier. Hereinafter this will be called short-circuit test. *c*, Recording simultaneously with that in Fig. 4, *a*, but secured with Amplifier 1. The voltage sensitivity here is insufficient to portray a clear, electrical record. 1 cm. = 1.5 millivolts. Deflection is upward when electrode in corpus tissue becomes electro-negative. *d*, Short-circuit test. Conditions same as for *c*. *e*, Approximately 1.5 minutes after hypodermic administration of pituitrin. Conditions same as for *e*. (Short-circuit value shown in *d*.) Contraction potentials marked (lower tracing), while pneumatic system (upper tracing) fails to display uterine contractions.

Following the hypodermic injection of 1 ampoule of surgical pituitrin, slight positive effects can be distinguished in the electrical record, as shown in Fig. 5, *c*, apparently as early as after only fifty-second interval. While the pneumatogram shows a continued rise in this figure, it is no greater than some others seen during a control period prior to the administration of the extract. The effect after the administration of pituitrin in this instance failed to become marked during a seven-minute period of observation.

CASE 4.—W. R., aged 24 years, para iii, gravida iii, married seven years. Menses: Twenty-eight- to thirty-five-day cycle, lasting ten days. Complaint: Premenstrual nervousness, beginning ten to fourteen days before the period. Pain in the lower

cavity, for here was no bag. It can be assumed that the fine short wires inserted do not stimulate contraction, for in skeletal muscle such wires have been used in hundreds of recordings in the absence of all contraction. Favoring this assumption also is the fact that in the dog's uterus some of the spontaneous contractions were readily visible before the two wires were inserted.

Evidently, then, with two wire electrodes in the fundus tissue of the human uterus, contraction voltages can be recorded. The curves are analogous to those secured when electrodes are inserted into the exposed uterus of the dog.

*Uterograms, Type B.*—One electrode in fundus tissue; the other in cervix (anterior or posterior lip). Bag in cavity of corpus uteri.

CASE 2.—S. H., aged 22 years, para i; gravida i. Menses: Regular twenty-eight-day cycle; last period four days ago. Present complaint: Vaginal discharge. Cervix cauterized six weeks previously.

Since the corpus is richer in muscle tissue, electrical pressure changes accompanying contractions will be greater than in the cervix. In common terms, the electrode ("negative") in the cervix tissue will be relatively "indifferent."

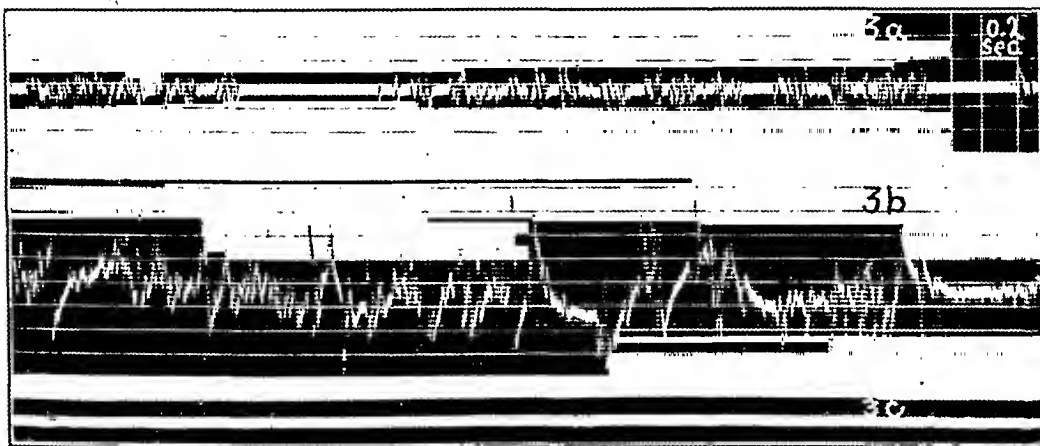


Fig. 3.—*a*. (Patient D. B.) Contraction voltages in human uterus recorded with string galvanometer alone. Both wire electrodes in fundus tissues. 1 cm. = 1 millivolt. *b*. Contraction voltages in same uterus, somewhat later, recorded with Amplifier 1. Both wire electrodes in fundus tissue. 1 cm. = 0.5 millivolt. (Deflection of string is upward when potential on grid lead becomes positive.) *c*. Control test, showing negative results when the conditions remain the same as for Fig. 3, *b*, except that wires have been withdrawn from the fundus tissue but remain in the sheath lying undisturbed in the uterine cavity. The tips of the leads are in contact, effecting a short-circuit.

Tonus in smooth muscle, so far as we know, has not heretofore been successfully measured in the intact animal. In skeletal muscle this has been accomplished by one of us using the present equipment.<sup>29, 30</sup> In Fig. 4, *a* (patient S. H.), we present an example (of which we have many) of the first electrical recording of tonus in smooth muscle; in this instance, the human uterus. Similar examples were secured (in 1935) with the dog's uterus (not published heretofore).

Fig. 4, *a* and *c* show mild but steady tonic contraction before pituitrin was administered (compare respectively with controls, Fig. 4, *b* and *d*). Shortly after the hypodermic administration of one ampoule of surgical pituitrin, contraction voltages increased markedly (Fig. 4, *e*); they now could be seen clearly even with the string galvanometer alone (not figured).

Contraction voltages are here enhanced after pituitrin, illustrating that the present electrical methods can be most useful in the study of oxytocic and other influences. In this one instance the mechanical system fails to show a clear-cut response after pituitrin, apparently not being sufficiently sensitive. This was improved during later studies, partly by increasing the air pressure in the system,

casation; but the extraet failed to quiet the patient's neuromuseular tensions, as tested in the abdominal museulature, and failed to relieve her complaints.

CASE 5.—H. M., aged 31 years, para i, gravida ii. Menses: Regular, thirty-day eyele. Menstruating now, without pain. Previous surgery: Appendectomy, perineorrhaphy. Complaint: Sterility since miscarriage one and one-half years previously. Physical examination: Negative.

Reeordings, both electrical and mechanical, indiate very marked uterine activity. One eyele, for example, lasting about twenty seonds, shows a microvoltage greatly exceeding 300. The uterine activity was present while the speeulum and volsellum were in place but was equally marked after these instruments were removed completely.

These reeords illustrate that very marked uterine contractions sometimes take place without pain; in this instance they occur during menstruation.

CASE 6.—N. I., aged 51 years. Climaeterie began four years ago, but a little bleeding at menstrual periods has persisted. Physical examination: Small atrophie corpus; normal cervix.

Tonus reeords are secured with this patient, resembling those shown in Fig. 4, a, but of higher microvoltage. The peak microvoltage is on the order of 8.0. No bag is inserted. When a physieian (Dr. L.) enters the room and carries on prolonged disussion with her, the contraction voltages increase markedly, at times on the order of 18 microvolts.

This illustrates electrical reeords of tonie uterine contraction during the late menopausal period and their augmentation during conversation about matters of moment (probably emotional stimulation).

CASE 7.—W. R., aged 37 years, para ii, gravida iii. Last menstrual period seven days previously. Menses: twenty-eight- to thirty-day eyele; duration five to seven days with moderate flow but pain on third day. Symptoms: Clots in menses, discharge, pain in right lower quadrant. Previous surgery: None. Physical examination: Suggests possible fibroid uterus.

The uterograms, both electrical and mechanical, show marked activity. Following the intramuseular administration of 3 e.e. of corpus luteum (H.W.D.), diminished activity is indicated for the first time on both systems simultaneously after about forty-five to sixty seconds (Fig. 6). Control tests were performed subsequently by withdrawing the electrode from the fundus tissue but leaving it in the sheath with negative results, for the string was quiet.

In this instance, information concerning the reaction time of the hormone was afforded simultaneously by the two systems of reeording.

CASE 8.—C. F., aged 35 years, para ii, gravida ii, six weeks post partum. Not nursing.

Both mechanical and electrical tracings show very marked uterine activity. Following the intramuseular administration of 3 e.e. of aqueous corpus luteum extract, a distinct diminution in the contraction voltages is discernible after about one minute. On the other hand, a diminution of contraction is not clearly discernible in the meechanical records until after about four minutes. A complete quieting fails to occur, as shown by either type of record.

For a control test, the wires were withdrawn a few millimeters, retracting the points from contact in the uterine tissues, while permitting them to remain within the sheath. The bag was left in place. The character of the voltages then secured in no way resembled what was seen previously, but evidently was due to liquid between the points, constituting a high impedance liquid contact. Following the experiment, the bag was removed and reinfated. A 20-minute test demonstrated the absence of any leak.

abdomen bilaterally passing to the back and legs intermittently since last delivery. Previous surgery: Appendectomy, perineorrhaphy. Physical examination: Uterus movable, retroverted; corrected by pessary.

Records of contraction of this patient's uterus were secured on the first occasion near the onset of her premenstrual tenseness. This was three weeks after her previous period but two weeks before the following one. The uterus showed marked contractions, as shown synchronously with the electrical and mechanical recording systems. Simultaneously, records were taken of contraction voltages in the abdominal musculature, which indicated that she was in a generally tense state at the time of measurement. While at first their magnitude was often on the order of 1 microvolt, after six minutes there was a marked increase of potentials on the order of six microvolts and after about another five minutes, the magnitude increased to peak microvoltages on the order of about 12.

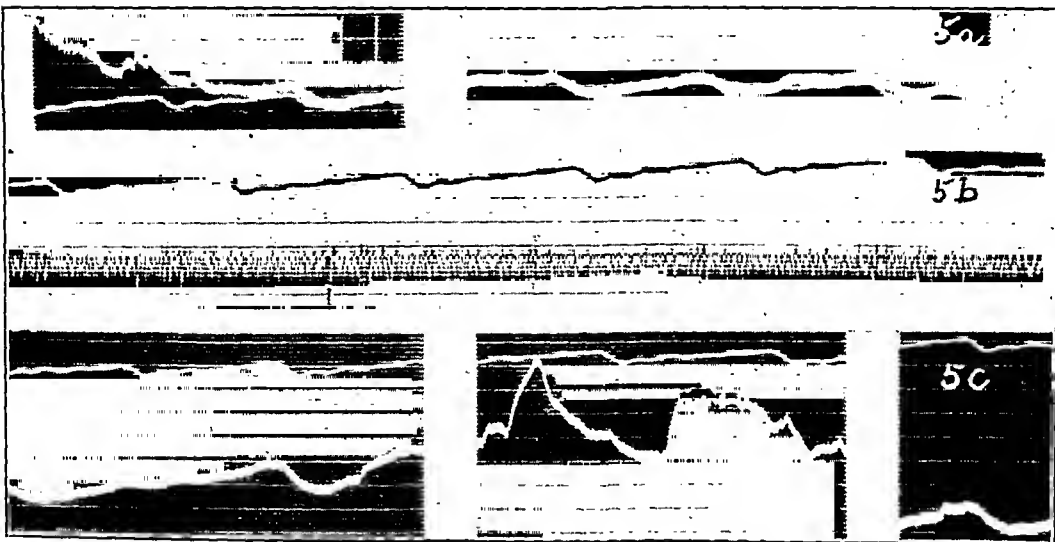


Fig. 5.—*a*. (Patient R. A.) Photographic tracings from contraction voltages (thicker line, Type B electrouterogram) and from bag in uterine cavity. Approximate coincidence of these tracings is shown in the latter portion of the photograph, which is quite unusual. Note the recording of arterial pulsation simultaneously in both records. An interval of about seventeen seconds elapses (white space) between the two photographs in *a*. 1 cm. = 5 millivolts. Deflection is upward when electrode in corpus tissue becomes electronegative. The control test upon short circuit is practically a straight line, as shown in *c*. *b*, Tonus tracing and mechanogram before pituitrin (Amplifier 2). *c*, Compare with *a*. Effects of pituitrin, administered hypodermically about twenty-five seconds before this recording was begun, become noticeable after a total increase of fifty seconds, for increased contraction voltages appear where indicated by the arrow. Upward deflection of electrical curve (the thicker line), signifies potential in lead in fundus is negative. Upward deflection of mechanogram indicates uterine contraction, which here is not very marked. 1 cm. = 5 millivolts. In the double recording shown in *c*, the electrical tracing appears to be the more sensitive indicator; for the mechanogram, although rising here, does not show much change following the administration of pituitrin. A positive result is shown on the electrical tracing as early as (approximately) forty-five seconds after the administration.

The second recording was made during the following month, twenty-one days after the onset of the last menstrual period. Progesterone had been administered two days previously (2 rabbit units intramuscularly). Both electrical and mechanical records reveal that the uterus was then relatively quiet. Nevertheless the patient's complaints were not diminished. That the patient was in a generally tense condition was suggested by the records from her abdominal muscles which showed microvoltages comparable with the larger ones recorded on the former occasion.

In this study, it is shown that the condition of premenstrual nervousness can be recorded objectively. Possibly the progesterone was responsible for the relatively quiet state of the uterus on the second oc-

requires one to two minutes. After about five minutes a marked and sustained tonic increase occurs which is sustained for about five minutes, followed by a fall in tonus and return of smaller contraction periods. The effects of pituitrin are noticed considerably earlier in the electrical than in the mechanical tracing. Clearer information regarding the length of individual contractions and the sustained tonus on which these contractions are superimposed is secured from the pneumatograms.

CASE 10.—K. M., aged 32 years, para iii, gravida iv. Menses: Regular, twenty-eight-day cycle, four days' duration, marked by flushes, backache and irritability for seven to ten days preceding the menstrual period. Next menstrual period expected in eight days. Physical examination: Uterus retroverted, corrected by pessary. Present complaint: Nervousness for ten days before menstrual period.

Electrouterograms, Type C, indicated a continued presence of steady tonus much greater at some times than at others. Tonus is present with the speculum in place, but also after it has been removed. About two and one-half minutes after the administration of pituitrin, a fivefold increase in microvoltage took place (as measured in the electrodes, using Amplifier 2). The change was from about 3 to 15 microvolts (maximum peaks), Fig. 7.

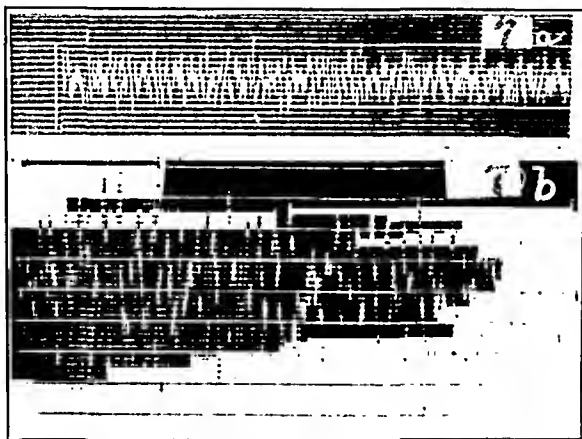


Fig. 7.—*a*. (Patient K. M.) Type C electroutrogram. Tonus recording in uterus during premenstrual nervousness before the administration of pituitrin. 3.5 mm. = 1 microvolt. *b*. Same: Two and one-half minutes after the administration of pituitrin. The control test (not shown) is of the same character as *a*, *b*.

In this instance, the tonus change following the administration of pituitrin was conveniently measurable in the electrical record (Amplifier 2). This was not true in all instances studied, for in one instance, where the mechanical record showed increased contraction, the tonus change was not shown in the electrical record made during the height of contraction.

A second recording with this patient was made about six months later on the twenty-third day of the twenty-eight-day cycle. She stated that this was on the second day of her premenstrual nervousness. Very marked contraction voltages (passing off the photographic record, much exceeding 200 microvolts and lasting from about two to twenty seconds) occur after intervals of relative quiet varying from about four to fourteen seconds. Following the subcutaneous administration of 3 c.c. of aqueous solution of corpus luteum extract, the electrical record shows quieting results which are distinct somewhat after one minute. The quiet interval now persists for sixteen seconds, followed by a contraction voltage lasting about three and one-half seconds, succeeded by a quiet interval of forty-four seconds. Meanwhile the mechanical record fails to give clear information.

Abdominal contraction voltages persist throughout on the order of 1-2 microvolts, showing no change after administration of the extract.

This study suggests that electrical recording, if sufficiently sensitive, is the procedure of choice to assay the reaction time of the effect of hormone and drugs on uterine activity.

*Uterograms: Type C.*—Both electrodes in cervical tissue.

CASE 9.—S. V., aged 21 years, para i, gravida i. Menses: Regular, twenty-eight-day cycle, three days' duration, moderate, severe cramping pain. Last menstrual period nineteen days previously. Previous surgery: Appendectomy. Present complaint (two weeks' duration): Lumbar backache, vaginal discharge, pruritus vulvae.

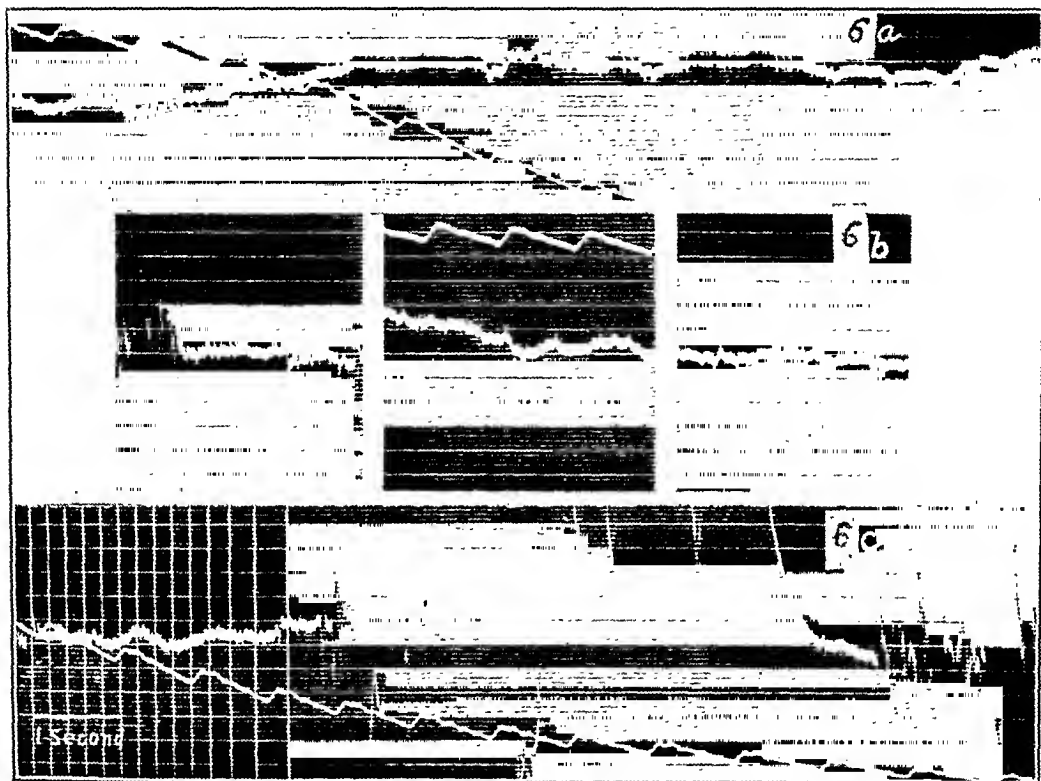


Fig. 6.—*a*. (Patient W. R.) Beginning about forty-five seconds or a little more after the intramuscular injection of an aqueous solution of corpus luteum extract, the uterus seems to be relaxing for a prolonged period. At this moment, the pneumatogram (thinner tracing) shows a sharp fall, passing off the photograph and remaining off or approximately so for the following one and one-half minutes; while the electrogram (thicker tracing) continues relatively quiet during the same period, aside from slight undulations, which probably indicate the persistence of moderate tonus. Type B electroutero-gram. 1 cm. = 65 microvolts. *b*. Control test about one minute prior to the administration of the hormone. Three frames are shown, each of which represents approximately three seconds of recording, while each of the two intervals or white spaces represents seventeen seconds. In the first frame, action-potentials are seen at the outset, but the pneumatogram is off the film on the contraction side, reappearing in the second frame. *c*. Another control test, beginning about one and one-half minutes prior to that shown in *b*. While the pneumatic tracing shows a decline, in the direction of relaxation, the voltage recordings are so marked as to pass off the film. Previous declines of the pneumatogram, like that shown here, likewise showed simultaneous marked action-potentials, in contrast with their absence in *a*.

At a time when the patient stated that she was having "uterine cramps," both mechanical and electrical tracings proved to be practically quiet. A simple intra-uterine bag was used for this mechanical recording. Following the administration of 1 ampoule of surgical pituitrin, the electrical record is the first to show changes, which become distinct after about three and one-half minutes. A distinct rise is seen in the mechanical tracing only after an additional eighty seconds. As seen on the mechanical record, a complete cycle of moderate contraction following this point



minute. Since previous investigators generally report no such brief intervals of response, these results will need to be confirmed in this respect.

5. For the definite determination of special conditions, such as premenstrual nervousness, objective methods of recording are presented. By the use of such objective methods, conclusions about the patient's state and the effects of hormones and other preparations can be achieved with greater probability.

6. The most convenient method for electrical recording and the one with least discomfort to the subject results from insertion of both electrodes into the lips of the cervix. For many studies, insertion of a bag can be omitted altogether.

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#### DISCUSSION

DR. WILLIAM DIECKMANN.—The authors are to be congratulated for developing a new method of investigating uterine motility. This method requires no intrauterine manipulation and is applicable to uteri of any size. These studies should eventually give us information as to the cause of dysmenorrhea, the onset of labor, and the cause of uterine inertia. The rapid response to pituitrin and progesterone is unusual and raises the question as to whether the response is the result of a drug action instead of hormone.

DR. JACOBSON (closing).—Dr. Dieckmann has commented upon the importance of a method to determine accurately the time when progesterone, adrenalin, pituitrin or some other extract or hormone first takes effect. To determine the time for the onset of effect of any particular extract would, of course, require a statistical study on many patients with frequent repetitions in each individual. This we have not done, but we have obtained sufficient data to introduce the problem and have shown how it can be solved. Accordingly, the aspect of our work which regards reaction and relaxation times of the uterus following the injections of various extracts or hormones will need to be confirmed.

During the April meeting of the American Physiological Society, Bender\* re-

\*Bender, M. B.: Proc. Am. Physiol. Soc., April 26, 1939.

CASE 11.—T. E., aged forty-two years, para iv, gravida v. Two years previously: Subtotal hysterectomy. Present complaint: Dizzy spells and leucorrhea. Physical examination: Negative except endocervicitis in cervical stump.

The recording is of interest as showing that with both leads in the cervix, contraction voltages of active type can be registered. This indicates that sufficient muscle tissue remains to afford such responses or that the currents are conducted from the uterine musculature.

### CONCLUSIONS

Decreased tonus and diminished contraction cycles in the nonpregnant uterus were seen following the intramuscular injection of an aqueous extract of corpus luteum. It is important to distinguish the interval at which relaxation begins to appear from the interval at which relaxation becomes for the first time complete, or as nearly so as is effected following the administration of the principle: We need to distinguish *beginning-relaxation time* from *complete-relaxation time*. If relaxation fails to become complete, and some contraction persists, it can be called partial-relaxation time. Recognizing these distinctions, we report instances where the beginning-relaxation time following the intramuscular administration of an aqueous solution of corpus luteum extract seemed detectable in so short a time as one minute. Since previous investigators (using no very sensitive indicators) report no such brief intervals, these results will need to be confirmed, since our studies were too few in number to warrant a conclusion on this point. It is perhaps pertinent that even much briefer contraction and relaxation times have been reported by Bender following the intravenous administration of physiologic extracts.<sup>31</sup>

For the study of premenstrual nervousness, the present methods afford means to secure objective records not alone of the uterine contractions or contraction voltages but also of the patient's nervousness (neuromuscular state). In this manner we are able to substitute for the patient's subjective or "psychic" complaints, a set of objective measurements.

In recapitulation, we conclude:

1. Activity of the human uterus can be successfully studied with the string galvanometer (or the oscillograph) plus amplifiers capable of measuring low voltages.
2. Physiologic studies of uterine activity can be made more completely if, in addition to the electrical measurements, mechanograms are made as well. Photographic tracings by electrical methods may show a striking correspondence or even parallelism with the mechanical tracings, but this depends upon what type of amplifier is employed.
3. Uterine tonus has been electrically measured in the present studies for the first time.
4. The effects of certain hormones and other agents on the uterus can be successfully detected by employing both mechanical and electrical measurements, each method supplementing the other. Following the intramuscular administration of an aqueous solution of corpus luteum extract, or the hypodermic administration of pituitrin, a relaxing or oxytocic effect (respectively) was detected in so short a time as one

ovulation is normally induced only by copulation. In normal rabbits, a nervous stimulation of the pituitary occurs on mating, producing the liberation of those hormones that cause ovulation.<sup>3</sup> This usually occurs from about ten to twelve hours after copulation. This timed phenomenon in the rabbit makes this animal very useful in the experimentation for the determination of early ovulation.

The maturation of the Graafian follicle, the expulsion of the egg, and the formation of the corpus luteum are all induced by the correct admixture of the gonadotropic hormones of the anterior pituitary. Any disturbance of this intricate and delicate mechanism will cause an imbalance of these hormones with the consequent sequelae to the organs of reception, the ovaries, with resultant menstrual disturbance.

In 1927, Aschheim and Zondek,<sup>4</sup> Smith and Engle,<sup>5</sup> demonstrated the interrelationship of the anterior pituitary and the gonads. Moore and Price<sup>6</sup> have presented a most complete and convincing evidence of the existence of this reciprocal relationship. The gonads are dependent upon the hormone of the anterior pituitary for a normal gametogenic output. Conversely, the gonads exert a controlling influence upon the anterior pituitary. Therefore, unusual activity of the gonadotropic hormones of the anterior pituitary may overstimulate the gonads. Conversely, the removal of a gonad may release its inhibitory factor on the gonadotropic hormone of the anterior pituitary.

Fevold and Hisaw,<sup>7</sup> and Wallen-Lawrence,<sup>8</sup> have reported the separation of both a true follicular-stimulating hormone, and an exclusively luteinizing factor from the pituitary tissues, while Foster and Fevold<sup>9</sup> have demonstrated the interrelationship of various gonadotropic hormones to follicular development, and ovulation in the juvenile rabbit.

The gonadotropic hormones can be demonstrated to be present and can be extracted from many different sources, such as the tissues of the anterior pituitary body, from the blood and urine of pregnant women, from human placenta, from urine of the castrate and menopausal woman, and from the blood serum of pregnant mares. These specific substances derived from different sources exhibit certain species differences, some of the most important of which are as follows:

1. Widespread follicle maturation<sup>10</sup> is obtained in the infantile mouse, rabbit, rat, *Macacus rhesus* monkey with the extracts of the anterior pituitary, castrate and menopausal urine, and pregnant mares' serum. The action of the hormone of pregnancy urine, however, is limited, in that few follicles develop which do not ovulate, but become hemorrhagic, or form corpora lutea with imprisoned ova. This is the basis for the Aschheim-Zondek test.

2. Follicular development in the ovaries of the hypophysectomized rats<sup>11</sup> is induced by the administration of the hormones extracted from the anterior pituitary, castrate and menopausal urine, and from the pregnant mares' serum, but not by the hormone extracted from pregnancy urine.

3. The extract of the anterior pituitary<sup>12</sup> and pregnant mares' serum causes the growth of the testes of the infantile rooster, and distinct growth of the comb, which the hormone from pregnancy urine does not do.

Leonard and Smith<sup>13</sup> found that pregnancy urine by itself will not produce maturation of the follicles, ovulation, and corpora lutea formation unless complemented by the gonadotropic factor in the urine of the castrates, of the menopausal, or the extract of the anterior pituitary.

Hamblen and others<sup>14</sup> have reported that no evidence exists that the gonadotropes derived from pregnancy urine, placenta or the anterior lobe of the pituitary, when

ported on the time of action of acetylcholine and of adrenalin when injected intravenously in the cat and monkey. Six seconds was the interval observed in the cat before the contraction of the denervated facial muscles. Fifteen seconds later a pronounced dilatation of the denervated pupil took place. Six seconds was the interval in the monkey before dilatation of the sympathectomized pupil showed the effect of adrenalin. Such brief times as Bender observed for the action of these agents when injected intravenously, while in no sense confirming our results in connection with the uterus, nevertheless harmonize with our present reports of very brief reaction and relaxation times of the uterus, following the administration of various extracts.

## STUDIES IN ARTIFICIAL OVULATION WITH THE HORMONE OF PREGNANT MARES' SERUM\*

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THE problem of sterility and infertility is a complex one, and its solution extends beyond mere conversation, explanation, and encouragement. The ultimate desideratum, fundamentally, in any given case should be to ascertain, if possible, which of the basic requisites for a successful fruition is at fault. Is it one of defective germ plasma, ovulation, or spermatogenesis; is it one due to some impediment of the passage of the gametes to the locale of fertilization; or, is it one due to an improper habitat for nidation or implantation, or one due to a combination of several, or all, of the aforementioned factors?

It is with the ovulatory factor that we are concerned in this communication.

When one considers the short span of life of the supposed "normal active liberated ovum" (for up to the present time we actually have no method of evaluating their normality), which today is practically certain to be less than twenty-four hours; and when one considers that the ovum is fertilizable for a still shorter time, the question of ovulation becomes of utmost importance. What is the time of ovulation in a given menstrual cycle, and in the cycle that follows? Does ovulation accompany every menstrual cycle?

From the data collected by Dickinson<sup>1</sup> and by Hartman,<sup>2</sup> and from our own investigation, the actual determination of the time of ovulation in the human being still remains a moot question. Of the many methods that have been used to ascertain the actual phenomenon of ovulation, none has been very definite as to its exact time in a given cycle. It is our impression, however, that ovulation in the human being occurs but once a month, and that conception is possible for only a few days in a menstrual cycle. This makes pregnancy in the human being much more of a hit and miss affair than in many animals, particularly those that have a definite estrus cycle.

In women, ovulation is ordinarily spontaneous, occurring in the absence of copulation, whereas in the rabbit, the cat, and the ferret,

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amination of the early cases reported in the German and French literature shows that some were also due to the staphylococcus, while others were simply rheumatic lesions. It became apparent gradually that there was a chronic form of bacterial endocarditis, often of insidious onset and prolonged duration, and usually caused by the *Streptococcus viridans*. At least a dozen of the early cases were probably of this type, although the lack of bacteriologic studies makes it difficult to establish the diagnosis. An excellent review of this subject has recently been made by Jensen.<sup>12</sup>

This chronic form, known in Germany as endocarditis lenta, was paradoxically labeled subacute bacterial endocarditis in this country and in England. The criteria formulated by the early clinicians for establishing the diagnosis are too well known for discussion. Briefly, they include: (1) the presence of valvular lesions (or a definite history of rheumatic heart disease), (2) fever, (3) embolic manifestations, and (4) positive blood cultures.

The disease is not common in pregnancy. One case has been reported for about every 200 cases of rheumatic heart disease in pregnancy, and if heart disease occurs in 1 per cent of all obstetric patients as claimed by several authorities, then subacute bacterial endocarditis might be expected once in 200,000 cases.

For the sake of brevity, the features of particular interest to the obstetrician in all of the reported cases are summarized in tabular form.

It will be seen from the table that the disease occurred in women from 18 to 35 years of age, and that parity was not a factor. Over half of the patients gave a definite rheumatic history, although only one-third had recognized heart lesions at the beginning of pregnancy. The onset of the disease was usually in the latter half of pregnancy, and 12 of the 18 patients progressed beyond the seventh month of gestation. Of the 12 viable infants, 10 survived, while death came to all of the mothers within six months after delivery. In 11 cases the diagnosis was confirmed by autopsy.

#### REPORT OF CASES

CASE 1.—A white multipara, aged 35, was first examined on April 7, 1931, during the fifth month of her pregnancy. She had had two normal deliveries at term ten and twelve years before, and two spontaneous abortions. During childhood, she was told that she had rheumatic heart disease, but there had been no symptoms of cardiac insufficiency since that time. She had typhoid fever at the age of twelve, and her appendix was removed in 1928.

The first half of her pregnancy was entirely uneventful. The initial physical examination revealed nothing unusual. The tonsils were small and not infected. The thyroid gland was not palpable. The lung fields were clear to percussion and auscultation. The cardiac rate and rhythm were normal, there were no murmurs, and the blood pressure was 110 systolic and 68 diastolic. The uterine fundus could be felt at the level of the umbilicus, and the pelvic measurements were normal. The urine contained no albumin or sugar.

Shortly after her first visit she developed a cold which persisted for three weeks. At this time a diagnosis of influenza was made, and she was kept in bed and given supportive treatment. During this illness a soft blowing systolic murmur was heard over the apex. She now developed chills and fever and a pain over the left kidney

employed singly or together, were capable of inducing ovulation or the formation of corpora lutea in the human being with estrogenic bleeding, even when given in huge doses.

It has been shown by Cole and Hart,<sup>15</sup> and by Zondek,<sup>16</sup> in 1930, that the serum of pregnant mares contains a gonadotropic-stimulating factor that causes ovarian stimulation such as described above, without further addition of a complementary factor.

Cole and Hart found that the gonadotropic hormone appears in the blood serum of the pregnant mare between the thirty-seventh and forty-second days of pregnancy, reaches a maximum between the fiftieth and eightieth days, and thereafter decreases and disappears between the one hundred and thirtieth and one hundred and eightieth days.

Zondek, in 1930, demonstrated that the hormone is excreted in the urine in only minute quantities. Glud and others<sup>17</sup> confirmed Cole and Hart's findings. Cole and Saunders<sup>18</sup> also showed that it disappears from the blood stream at the time that the greatest concentration of the follicular hormone appears in the urine.

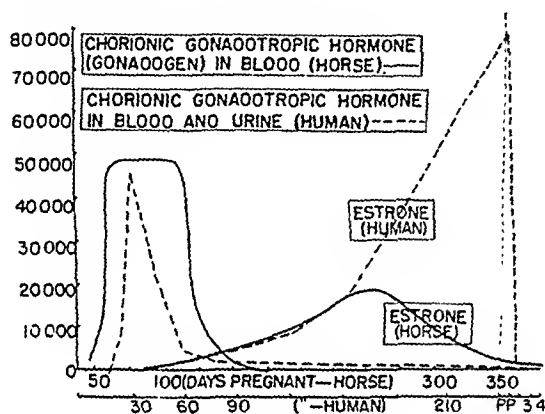


Chart 1.—Graph showing the concentration of the hormones in pregnant mares' serum and in the pregnant human serum and urine. (Modified from Cole and Saunders.)

In human pregnancy, on the other hand, the gonadotropic hormone can be demonstrated to exist both in the blood serum and in the urine. Both of these have been shown by others<sup>19</sup> and by us<sup>20</sup> to be secreted and excreted with characteristic concentration for the normal.

In the pregnant mare, the gonadotropic hormone is found in the plasma, endometrium, chorion, and maternal pituitary.<sup>20</sup> It is not readily excreted by the kidneys in the mare,<sup>15</sup> rat, monkey,<sup>10a</sup> castrated rabbit, and gelding.<sup>21</sup> It is not stored in the uterus, spleen, lungs, kidneys, and liver, and since the rate of disappearance is the same in the castrate as in the noncastrate rabbit,<sup>21</sup> it is, hence, impossible, that the gonads play a significant role in its destruction.

In the human pregnant individual it is well known that prolactin passes the kidneys with ease. The concentration of the hormone in the blood serum fairly well agrees with that in the urine. Anterior pituitary-like hormone has been shown to be excreted in the urine of the rabbit,<sup>22</sup> rats, and monkeys,<sup>10a</sup> after the animals have been intravenously injected with the hormone of pregnancy urine. The same has been demonstrated in the nonpregnant woman who had been transfused from a pregnant woman.<sup>23</sup>

Due to this property of the hormone of pregnant mares' serum, of remaining in the blood stream until it is destroyed, and not being ex-

creted in the urine, it allows its action on the gonads to approximate more closely a continuous one, than does that of the readily excreted anterior pituitary-like hormone.

We had injected, intravenously, 200 units of the hormone of pregnant mares' serum, in one single dose, to each of two amenorrhoeic cases, respectively of  $6\frac{1}{2}$  and 2 years' duration, both of whom had negative estrin and prolactin in the blood and urine before the administration of this hormone. We had not recovered any of the hormone as such in the urine after eighteen hours to five days, although concentrations of diminishing amounts were found in the blood serum taken daily over the same period. Complete data of these findings will be published in a later communication.

In general, the biologic effects produced by the hormone of pregnant mares' serum when injected into animals are more in the nature of a physiologic response than that produced by the hormone of the pregnancy urine. In this respect, the gonadotropic-stimulating action of the pregnant mares' serum more closely resembles the gonadotropic effects produced by the animals' own hypophysis. It was found that the injection of the hormone of pregnant mares' serum in young ewes produced ovulation during an anestrus season. A second dosage given seventeen days later resulted in a second ovulation with estrus, resulting in pregnancy when the ewes were mated.<sup>24</sup> Similarly, young sows when injected with the hormone of pregnant mares' serum produced ovulation at estrus, and pregnancy followed mating. Cows receiving large doses showed greatly enlarged ovaries when autopsied six days later.<sup>25</sup>

Experiments on the stallion, bull and bear indicate that this hormone increases the activity of the Leydig cells of the testes resulting in enlargement of the seminal vesicles and prostate.<sup>26</sup> We have found this to be of help, clinically, in cases of oligospermia and necropermia, increasing the number of motile sperm, in several instances 100 per cent, by the administration of the hormone of pregnant mares' serum in 10 U\* doses every other day intramuscularly.

Follicular stimulation and development of the secondary sex characteristics with reddening of the skin areas can be produced in the immature rhesus monkey by the administration of this hormone.<sup>27</sup> Hartman<sup>28</sup> has been able to produce ovulation in anovulatory adult monkeys. He was able to demonstrate the ovum thus produced with the hormone of pregnant mares' serum.

We have found that follicular formation can be visualized two hours after the intravenous injection of 2 U of the hormone of pregnant mares' serum, administered to an immature rabbit weighing  $2\frac{3}{4}$  pounds, ovulation taking place as early as eight hours. In the immature *Macacus rhesus* monkey, weighing  $7\frac{1}{2}$  pounds, after daily intramuscular injection of 5 U of this hormone, we have found on the third day, reddened external genitalia and enlarged nipples, and on laparotomy on the seventh day, enlargement of the ovaries to about 8 times their original size, with diffuse follicular stimulation and hemorrhages.

\*U, the Cartland and Nelson Unit—the minimum total dose of hormone which, administered to twenty-one- to twenty-three-day-old rats, weighing 35 to 45 gm., in three equal subcutaneous injections at daily intervals, will produce at autopsy, ninety-six hours after the first injection, a mean ovarian weight of 65 mg. which is four to five times that of the controls.

Siegmund,<sup>29</sup> Moricard and Saulnier,<sup>30</sup> and Watson and others,<sup>31</sup> were able to stimulate follicular development in women with the hormone of pregnant mares' serum, but could not show ovulation in any of their cases. In 1937, Davis and Koff,<sup>32</sup> were able to demonstrate by laparotomy that ovulation could be produced by the intravenous administration of this hormone. This, combined with our growing conviction that many cases of sterility in women, who were bleeding cyclicly, were due to failure of ovulation, prompted us to investigate this new gonadotropic substance.

### METHODS

1. An attempt was made to corroborate the work of Davis and Koff.
2. Where ovarian response could not be studied by laparotomy, it was possible to do so by the endometrial response using repeated suction biopsies of the endometrium before and after the administration of the hormone.
3. Kymographic recordings following repeated uterine insufflations were made before and after the administration of the hormone, in cases of amenorrhea, upon which estrin and prolan were determined.

In this communication we will limit ourselves to observations made by the first method.

The patients who were laparotomized were not chosen especially on account of their menstrual disturbances, but were those upon whom some pelvic operative procedure had been contemplated.

The hormone, a protein derivative, was administered to all of the patients in one single dose intravenously, having first tested the patient for protein sensitivity both by the intradermal and ophthalmic methods. In but one case was there a latent reaction to the hormone which manifested itself in an urticaria on the eighth day after the administration of the serum. We refrained from giving the substance to a number of patients who developed wheals after the intradermal test.

Endometrial biopsies were obtained prior to the administration of the hormone in all but two patients, these being virgin. As noted in the table, the amount of hormone used and the interval of time elapsing between the time of administration and laparotomy varied. The ovaries were examined in situ, and were either totally, or sectionally, removed for histologic examination.

### DISCUSSION

As pointed out recently by Novak,<sup>35</sup> it is as difficult to differentiate the walls of an early corpus luteum from that of a maturing follicle as it is to differentiate the predecidua endometrium of a nonpregnant woman from that of a genuine early decidua. However, the criteria followed as to the age of the corpora lutea was the same as that used by Davis and Koff, namely, that of Allen, Pratt, Newell and Bland,<sup>33</sup> the salient features of which are: Macroscopically, as found in our investigation, the corpora were of varying sizes, measuring from 10 mm. to 30 mm., the majority of which showed recent rupture points, with a bloody fluid or gel filling the cavity. Microscopically, the stages of the corpora can be divided into three:

1. *The Stage of Formation.*—(a) The early formative stage shows a slight luteal transformation of the former granulosa cells. The latter are more follicular than luteal. There is no hemorrhage in the cavity, and there is an absence of fibroblasts



in the inner layers of the cells, which in this report is interpreted as indicating at least the first day of development after rupture. (b) The late formative stage displays many fibroblasts that have migrated through the luteal layers into the central cavity, indicating the second, or perhaps, the third day of development.

2. *Stage of Maturity*.—The theca externa and interna have reached their highest development. The theca interna contains some lipoid substances and the externa consists of concentrically arranged fibers and fusiform cells and contains large blood vessels. These two connective tissue capsules are usually referred to as the wreath. The follicular cells show considerable amount of proliferation; but the luteal cells have not yet developed the yellowish characteristics of the older cells.

3. *Stage of Retrogression*.—More connective tissue than the previous stage, and this has invaded the degenerated epithelium. The cavity is smaller than in the stage of maturity, and there are present large quantities of yellowish pigment. Many of the cells contain lipoid substance. The theca interna is increased in size.

Our results can be divided into four groups.

*Group 1*.—Those upon whom there was no ovarian response. In this group there were 6 patients who showed neither follicular stimulation nor evidence of recent ovulation.

*Group 2*.—Those who showed a diffuse follicular enlargement. In this group there were 5 cases.

*Group 3*.—Those who showed the same reaction as Group 2, as well as the presence of a current corpus luteum, but no evidence of recent ovulation. Of these there were 3 cases.

*Group 4*.—Those who showed follicular stimulation and evidence of recent ovulation. Of these there were 16 cases. Correlating our criteria as to the age of the corpora lutea, and the time elapsing between injection and operation, recent ovulations and follicular stimulations were diagnosed histologically as having occurred in 53 per cent of the patients.

It will be noted that most of the ovulations occurred in the first half of the cycle. Several occurred in the latter half.

In one case of amenorrhea of seven months' duration, no evidence of ovulation, either recent or current, was found, but there was diffuse follicular stimulation. In this case, there was a thickened tunica albuginea, of an almost leathery consistency. Might this not be the cause of the failure of ovulation in this case?

In two cases of cystic glandular hyperplasia, one showed a recent and current corpus luteum, while the other showed no evidence of recent ovulation. Both of the patients were admitted with a history of profuse irregular bleeding.

Endometrial biopsies taken on admission of patients bleeding, and with irregular cycles, showed various mucosal patterns, and responded differently to this gonadotropic hormone. It is interesting to note from the table that all phases of the menstrual cycle can be seen at any period in the interval. It has been our procedure in obtaining these biopsies to curette all the walls of the uterus, particularly the fundal area. Our histologic interpretations were made by our findings in the compact and spongiosa layer of the mucosa. Not infrequently, one finds a mixed pattern. In this group our conclusions were drawn from the predominant phase prevailing.

The age of the patients varied, although the younger the group, the better the response.

Why some ovaries would respond, and others would not, can be best explained, in our opinion, first, by the fact that in not a few cases were the ovaries the sequelae of chronic pelvic infection; second, that

some were approaching the menopause; third, that it can be theorized that there are variations in ovarian receptivity and refractivity in certain individuals to the gonadotropic hormone, be they exogenous or endogenous in character.

TABLE I

	CASE	AGE	MENSES		ENDOMETRIAL BIOPSY	AMOUNT OF P.M.S. <sup>1</sup> INJECTION	TIME TO OPER. HOURS	OVULA- TION		FOLLICLES		
			INTERVAL	DAY OF CYCLE				RECENT	CURRENT	MATURE OR MATURING		ATRETIC
1	42013	42	2-3 mo.	Bleed- ing	Late proliferative	60 U	43	0	0	**		*
2	42210	32	Amen- orrhea	7 mo.	Early proliferative	30 U	48	0	0	***Hem.		*
3	42326	18	28 days	5	Early proliferative	60 U	48	1	1	*		
4	42333	40	28 days	6 wk. prior to adm.		60 U	46	1	1			
5	42393	38	28 days	12	Late proliferative	60 U	19	2	1	**		
6	42445	30	Irreg.	10	Early proliferative	60 U	18	1	1	**		*
7	42409	23	28 days	6 wk. prior to adm.	Late secretory	60 U	18	0	1	*Hem.		*
8	42411	28	28 days	4	Early secretory	60 U	18	0	1	**Hem.		
9	42557	24	28 days	11	Late proliferative	60 U	21	2	1			
10	42563	26	Irreg.	Bleed- ing	Early secretory	60 U	22	0	1	**		
11	42640	31	28	9	Early secretory	60 U	22	1	1	**		
12	42684	17	28	10	Early proliferative	60 U	18	1	1			
13	42693	24	Irreg.	7	Early proliferative	60 U	24	0	1	**Hem.		
14	42730	40	Irreg.	Bleed- ing	Degenerated pla- cental tissue	60 U	17	0	1	**		
15	42788	22	28	16	Early secretory	60 U	23	0	1	***Hem.		
16	42791	32	28	Bleed- ing	Hyperplasia; secre- tory	60 U	24	0	0			
17	42877	46	Irreg.	Bleed- ing	Early proliferative	60 U	22	2	0	**Hem.		*
18	42894	28	21	16	Cystic hyperplasia; secretory	60 U	42	1	1	**Hem.		
19	42940	33	28	16	Late proliferative	60 U	24	0	1	***Hem.		
20	42987	37	Irreg.	Bleed- ing	Cystic glandular hyperplasia	50 U	22	0	1	**Hem.		
21	43028	33	28	10	Early proliferative	60 U	20	1	0	***Hem.		*
22	43047	26	28	12	Late proliferative	40 U	21	0	1	**		
23	43066	24	28	6	Early proliferative	60 U	22	2	1			
24	43121	28	28	14	Late proliferative	60 U	21	1	1	***Hem.		*
25	43241	47	Meno- pause		Atrophic endome- trium	60 U	20	0	0	***Hem.		
26	43295	40	28	Bleed- ing	Early proliferative	60 U	20	1	1			
27	10478	16	28	11	Cystic glandular hyperplasia	60 U	25	1	0	***Hem.		
28	18672	38	28	16		60 U	23	1	1			
29	18945	33	26	8	Early proliferative	60 U	35	2	1	**Hem.		*
30	19052	46	Irreg.	Bleed- ing	Early proliferative	90 U	21	0	0	Dermoid cyst		

<sup>1</sup>Pregnant mares' serum.

\*Number of follicles present.

As was shown by Hartman<sup>34</sup> in his work with this hormone on the adult monkey, and in this series on the human being, the commonest lesion consisted of a diffuse stimulation of the follicles. This was present in almost every instance where a response had occurred. It manifested itself in a granulosa cell proliferation of several layers of thickness with mitosis, cytolytic degeneration of the inner layers of the cells, perifollicular and intrafollicular hemorrhage. The question arises, in these cases, as to whether in the ovaries, if allowed to remain in situ

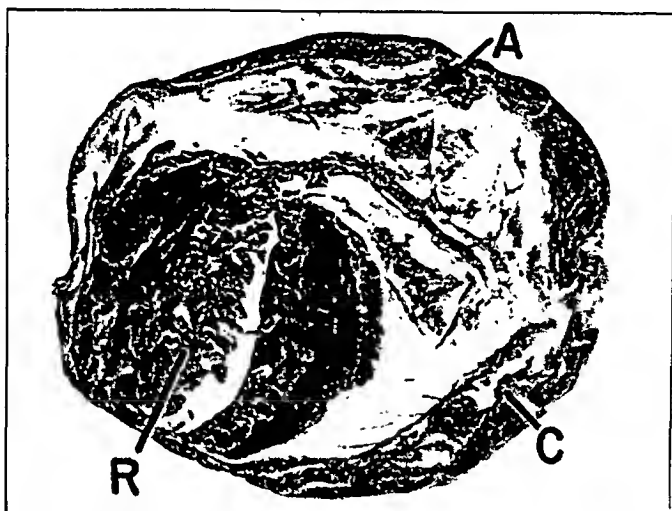


Fig. 1.—Case 42445. Recent (*R*), current (*C*), and atretic (*A*) follicles. The wall of the corpus appears completely folded. There was some hemorrhage in the folds and the cavity contained a small amount of fluid and has not redistended. The walls were pale. Eighteen hours after the administration of the hormone of pregnant mares' serum.

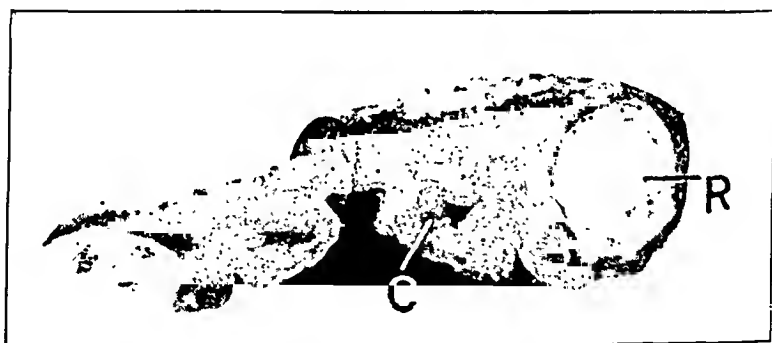


Fig. 2.—Case 43028. Recent (*R*) and current (*C*) ovulations. Note the hemorrhagic character of the recently ruptured follicle which also contains some gelatinous fluid. Twenty hours after the administration of the hormone of pregnant mares' serum.

for a longer period, would the follicles so produced progress further to ovulation, or would regression take place with the formation of atretic follicles?

In the adult monkey, where ovaries were so stimulated and allowed to remain in situ, not infrequently, the follicle would regress to that of a normal histologic structure, ovulate of its own gonadotropic stimulation, and the monkey would occasionally conceive.<sup>34</sup> The first part of

this phenomenon we have repeated in the immature *Macacus rhesus* monkey. Obviously this cannot be demonstrated in the human being. If one can use the analogy of the monkey, however, it can be stated that the manifestly deleterious action of this hormone is only temporary and that recovery is prompt and complete.



Fig. 3.—Case 42557. Gross view of a rupture point (R) of a recent ovulation not yet healed over. Twenty-one hours after the injection of the hormone of pregnant mares' serum.



Fig. 4.—Case 18672. The current (C) corpus luteum is well organized and contains an old hemorrhage. Twenty-three hours after the administration of the hormone of pregnant mares' serum.

The action of this hormone, when effective, is very rapid, as shown both in the rodent and in the primate. Follicular maturation, ovulation, and corpora lutea formation can take place within twenty-four hours, and in several instances, in the human being, more than one ovulation can take place at the same time, as the result of the administration of this potent hormone.

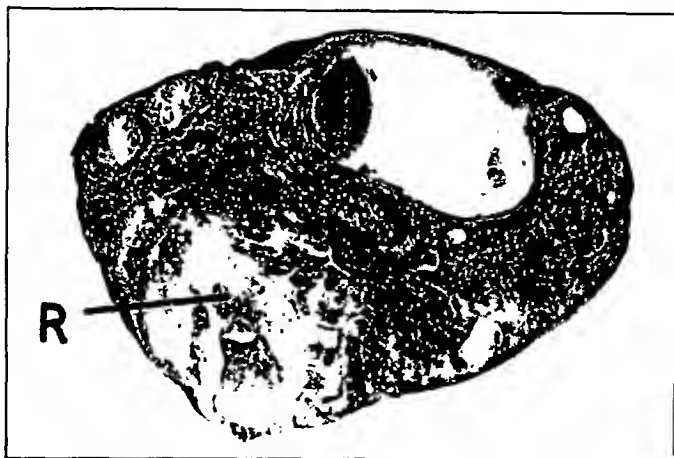


Fig. 5.—Case 18672. Note hemorrhagic cystic follicles. The lutein wall of the recent ruptured follicle (*R*) is not well developed. The cavity is distended and filled with a bloody gel.

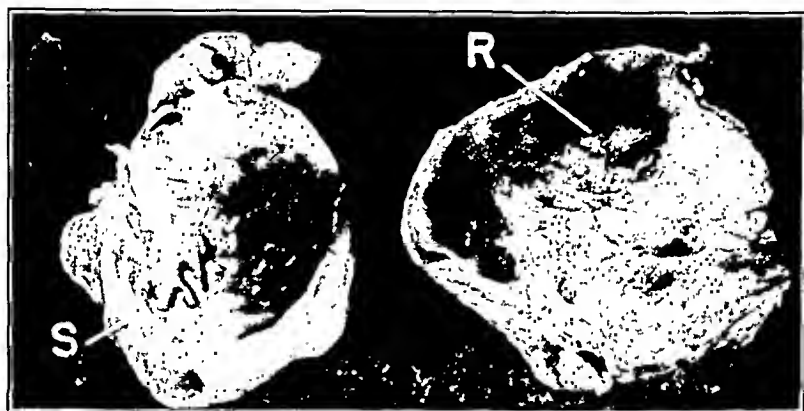


Fig. 6.—Case 42894. Gross appearance of a recently ruptured (*R*) follicle, the walls of which have collapsed, the cavity being filled with a blood-tinged fluid. Stigma (*S*) present. Several stimulated follicles also present. Forty-two hours after the administration of the hormone of pregnant mares' serum.

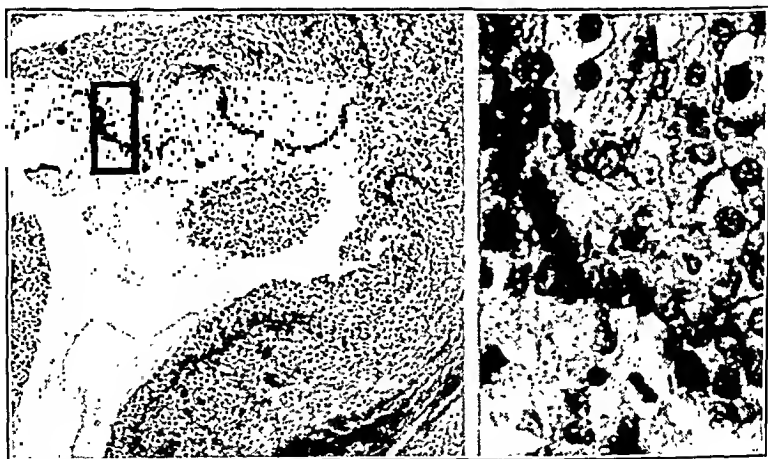


Fig. 7.—Case 42445. Eighteen hours after intravenous injection of sixty units of gonadogen. Endometrial biopsy showed early proliferative stage. Early corpus luteum of proliferation. Note arrangement of three layers. Cells of theca interna filled with light staining lipid; capillaries dilated and filled with blood. Mitosis of granulosa with streaming of coagulum. No fibroblasts in central cavity. ( $\times 95$ .)

Mitosis and coagulum which may be interpreted as evidence of secretion. ( $\times 800$ .)

From a clinical standpoint, this hormone is still too new to permit an accurate evaluation as to its efficacy in gynecologic endocrine problems, particularly those due to inadequate pituitary stimulation.



Fig. 8.—Case 42393. Nineteen hours after intravenous injection of 60 units of gonadogen. Recent rupture point filled with blood-tinged gelatinous plug. The rupture point has not yet healed by cell growth. Endometrial biopsy showed late proliferative stage. ( $\times 20$ .)



Fig. 9.—Case 42877. Twenty-two hours after intravenous injection of gonadogen. Early formative or proliferative stage. No hemorrhage or fibroblasts in central cavity. Slight transformation of the granulosa cells. Beginning of vascularization of the luteal layer. Endometrial biopsy showed early proliferative stage. ( $\times 110$ .)

From the preliminary investigations of others and one of us (S. L. S.), it seems to be of use in those cases of primary and secondary amenorrhea, which are due to failure of maturation of the follicles with corpus luteum formation, and in those cases of anovulatory bleeding due to the failure of mature follicles to ovulate. In the treatment of these con-

ditions, one should plan his injections so that he can imitate the normal phases of the cycle, for the time factor is important in the response of organs to hormones. After all, the object of treatment with a gonadotropic substance is to stimulate the ovary to normal function, and the ovarian changes should not be so rapid that the uterus cannot keep pace with the ovary.

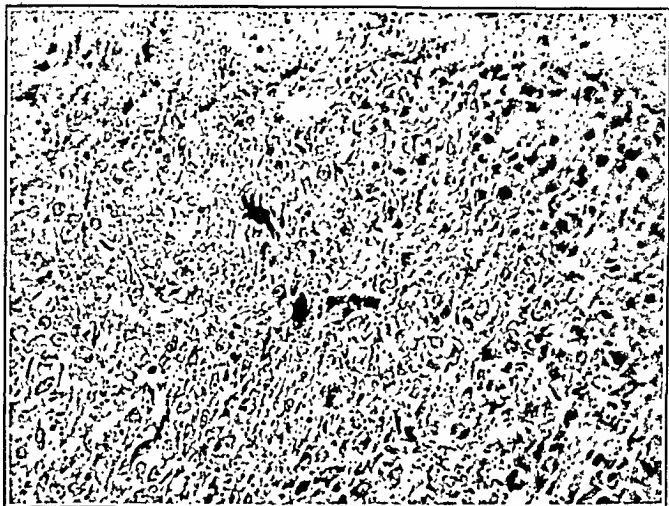


Fig. 10.—Case 18945. Thirty-five hours after injection of 60 units of gonadogen. Late formative stage. Further luteal transformation of granulosa cells; only a few fibroblasts invading the central cavity. Vascularization was not far advanced. No wreath formation. Endometrial biopsy showed early proliferative stage. ( $\times 250$ .)

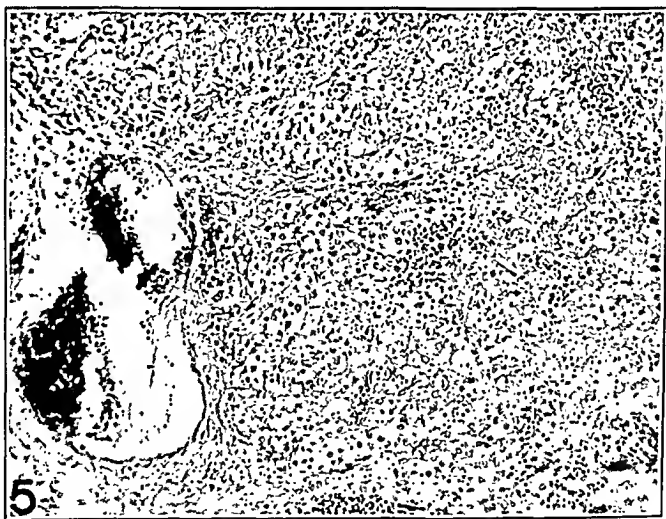


Fig. 11.—Case 42333. Forty-six hours after the injection of 60 units of gonadogen. Late formative stage. Obliteration of dividing line between granulosa cells and lutein layer. Transformation of granulosa further advanced. Hemorrhage between cell folds and in the central cavity. Migration of fibroblasts through inner layer of luteal cells. Endometrial biopsy showed early proliferative stage. ( $\times 190$ .)

We are slowly accumulating evidence as to the value, clinically, of this hormone. In several instances where the genital secondary characteristics have developed normally, and in the presence of primary or secondary amenorrhea, with an endometrium pattern of an early proliferative stage, and hormonal determinations showing negative estrin

area. A catheterized urine specimen showed numerous pus cells and many staphylococci, and a diagnosis of pyelitis was made.

She entered a private hospital on April 30, 1931, and had a bilateral lavage of the kidney pelves, with instillation of silver nitrate. The consulting urologist reported no acute cystitis, and sterile urine cultures, although the urinary sediment contained a few red blood cells, pus cells, and casts. A blood count at this time showed 72 per cent hemoglobin, a red blood count of 4,430,000, and a white cell count of 13,950 with 89 per cent polymorphonuclears.

She continued to have chills and a swinging fever. A blood culture taken on May 5 showed a growth of *Streptococcus viridans*, and a second blood count showed a slight drop in the hemoglobin and red cell count, and a slight rise in the white cell count. Examination of the heart at this time revealed a definite mitral stenosis and insufficiency. The diagnosis became subacute *Streptococcus viridans* endocarditis.

Aside from supportive treatment, the only therapy was the use of sorocin intravenously. She continued a downward course, with daily fluctuations of temperature ranging from 96 to 106° F. On May 22, 1931 (six and one-half months pregnant), spontaneous labor began, and she delivered a two pound living male fetus which survived for one and one-half hours.

The patient died on the tenth day post partum, seven weeks after the onset of her illness. Permission for autopsy was not granted.

CASE 2.—A 30-year-old white female entered the Alameda County Hospital on Jan. 28, 1937, complaining of cough and fever for the past month.

Until she was 18 years of age she had eight to ten severe attacks of tonsillitis a year, and said that she had "mild growing pains" during adolescence. She had two children, aged 8 and 6 years, and toward the latter part of her second pregnancy she had noticed increasing dyspnea on exertion. This subsided after the delivery, but returned about one year ago and has become progressively more severe. The shortness of breath did not interfere with her usual activities until the onset of her present illness. The remainder of her past medical history is of no significance.

Her last normal menstrual period began on Oct. 20, 1936. Moderate nausea and vomiting and slight soreness of the breasts followed, but her general health was good until one month before entry. At this time (Jan. 1, 1937) she contracted an upper respiratory infection with acute sinusitis, frontal headaches, laryngitis, and cough. Orthopnea ensued, the cough became worse, and she began to raise frothy, blood-tinged sputum. For the past two weeks there had been daily fever (up to 102° F.) and chills. One week before entry, small red spots on the wrists and painful nodules on the fingers appeared.

Examination disclosed a very pale, dyspneic and slightly cyanotic woman of average bodily build. The temperature was 100.4° F., pulse rate 120, respiratory rate 26, and blood pressure 92 systolic over 60 diastolic. On both wrists were numerous petechiae, and there were several tender nodes on the lateral aspects of the fingers. Her voice was husky, the pharynx was moderately injected, and both tonsils were enlarged and scarred. Moist râles could be heard over the bases of the lungs, and there were inspiratory wheezes. The apex beat of the heart was displaced considerably to the left and over this area could be felt a systolic thrill. The rhythm was regular and rapid, the second pulmonic sound was accentuated, and over the apical area could be heard a faint presystolic murmur. The liver edge and the spleen were just palpable, and the uterine fundus could be felt 5 cm. above the symphysis. The findings on pelvic examination were compatible with a pregnancy of three months' duration.

The hemoglobin was 54 per cent (9.12 gm.); the red blood cell count 2,750,000; white blood cell count 55,100 with 97 per cent polymorphonuclear cells, one-fourth being nonsegmented forms. Anisocytosis, poikilocytosis and occasional nucleated red blood cells were present. The blood urea nitrogen was 23 mg. per cent. The Wassermann tests were negative. The initial urine examination showed nothing abnormal.

Blood cultures were taken and after seventy-two hours showed a growth of *Streptococcus viridans*. An x-ray of the chest revealed nothing unusual in the lung



3. Conservative and controlled clinical observations will determine the ultimate efficacy of this new hormone. Clinically, it may prove of value in those cases where gonadotropic stimulation appears desirable.

4. Being a protein derivative, prudent care should be exercised in the administration of this potent hormone.

5. We can, on the whole, substantiate the work of Davis and Koff.

We wish to express gratitude to the Upjohn Company for making this investigation possible by the liberal supply of gonadogen, the hormone of pregnant mares' serum used, and for their financial assistance. We also wish to thank Lester Bergman, M.A., for his assistance in the animal experimentation, and Henry Feintueh, M.D., Josephine Bearss, Margaret Kopicki, B.A., and A. P. Chiaramonte, B.A., for their assistance in the Laboratory at the Unity Hospital.

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#### DISCUSSION

DR. GEORGE F. CARTLAND, KALAMAZOO, MICH. (by invitation).—Dr. Siegler's observations constitute an excellent confirmation of the work of Davis and Koff in demonstrating that the mare serum hormone is capable of inducing ovulation in the human being. Since the dosage and route of administration were practically constant in this series, the variation in response may be interpreted as indicating individual differences in ovarian receptivity to the gonadotropic hormone. This has its parallel in animal experiments.

In the case of the immature rat of constant age, variations in ovarian receptivity are largely eliminated. The uniformity of ovarian response at various doses constitutes an accurate method of biologic standardization. With approximately 0.1

and negative prolan, menstruation was established after the administration of 10 U doses for three consecutive days, followed by intravenous injection of 30U. Where success was not obtained after a series, a second series was begun after an interval of two weeks.

Those cases of primary or secondary amenorrhea showing a persistent positive prolan and negative estrin in their hormonal determinations, no matter what the endometrial pattern reveals, were all refractive to any type of gonadotropic stimulation. We have been successful in initiating fairly regular menstrual periods of the secretory type in several patients with anovulatory bleedings, one of whom has conceived, and delivered on April 14, 1938, of a living normal female infant of thirty-six weeks' gestation, weighing 4¾ pounds, after having been sterile for six years. Endometrial biopsies taken at many episodes of bleeding never showed an architecture of the secretory phase prior to the administration of this hormone.

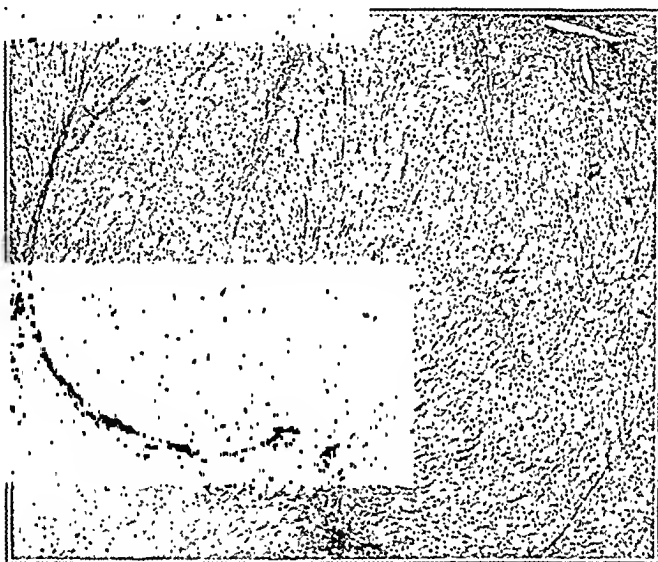


Fig. 12.—Case 42326. Forty-eight hours after injection of 60 units of gonadogen. Stage of maturity. Fairly well-developed fibroblast wreath separating luteal cells from central cavity. Lutein cells fairly well developed. ( $\times 80$ .)

Many of our patients received one single intravenous dose of 60 U, others, divided doses of 10 or 20 U intramuscularly daily or every other day, and still others, a combination of the intramuscular and intravenous type of injection. The latter method we believe to be the most efficacious.

It is quite possible that our failures may be due to our inability to estimate the correct dosage. One must always bear in mind, however, in the treatment of these cases, the individual receptivity and refractivity of the ovaries being so stimulated.

#### CONCLUSIONS

1. In many respects the gonadotropic fraction of the pregnant mares' serum closely resembles the gonadotropic activity of the extracts of the anterior pituitary.

2. Artificial ovulation has been shown to have been produced in the rabbit, the monkey, and the human being, by the use of the hormone of pregnant mares' serum.

follicle function and corpora lutea are conspicuously absent. On the other hand, if a similar series of cases were selected where the hormones of pregnant mare serum were injected a day or two after the regular menstrual cycle and the laparotomy were done within one, two, or three days, one should also be in a better position to speak of the production of fresh corpora lutea.

Another factor complicates the interpretation of these cases. The ovaries associated with pelvic inflammation, fibroids, and other conditions, frequently show corpora lutea in various stages of development and regression without these having been induced by a hormonal injection.

Whether the hormone of mares' serum will start a menstrual cycle in cases of amenorrhea has not been mentioned by Siegler. If that can be accomplished we shall have an effect comparable to that which is induced by a physical agency such as the x-rays and, in my experience also, by small doses of radium.

I was pleased to hear Siegler emphasize the importance of making a sensitization test by the intradermal and ophthalmologic application because there have been serious reactions. It is important if one is going to use the serum not to take it for granted that the patient will tolerate it but always to make certain beforehand of her reactions.

DR. JACOB S. BEILLY.—Bland and Mazer state that a great number of women seen with sterility present an anovulatory cycle. I believe that these conditions demand some form of treatment, and pregnant mares' serum seems to suggest a possible avenue of relief.

Experimental ovulation in primates has been only recently accomplished by Hisaw, who was able to produce ovulation in the monkey. He appears to have used a luteinizing as well as a follicle-stimulating hormone preparation. The synergistic action of these two combined factors, which arise from the anterior pituitary body, resulted in ovulation. Pregnant mares' serum has the biologic effect of this combination.

Our own experience with the gonadotropic hormone of the pregnant mares' serum, however, has not been as gratifying as we had anticipated, and I am of the opinion that the clinical application of this very potent preparation is not yet well known. Our assay of the preparation does not seem to hold up with the assay of the product as it originally leaves the factory. It is likely, because of its protein nature, that there is considerable deterioration between the time it is assayed at the factory and the time we are ready to use it. Having re-assayed it, we found marked differences in its potency.

DR. SIEGLER (closing).—I do feel that the hormone of pregnant mares' serum is of use in the treatment of sterile patients, particularly those on whom one diagnoses anovulatory bleeding or pituitary insufficiency as the causative factor. One can with reasonable assurance state from our histologic examination in this series that follicles are stimulated, mature, and ovulate as a result of the administration of this hormone, which is physiologically and biologically different from the hormone of pregnancy urine.

Ostensibly, there are many normal menstruating women who have episodes of anovulatory bleeding, and will, of course, be sterile during these episodes. But I hesitate to agree with Dr. Rubin that the cases of pregnancy cited were the result of just such occurrences. One of these patients, sterile for six years, received all forms of organotherapy, including x-ray treatment to the pituitary and ovaries for her anovulatory bleeding, with no change in the endometrial architecture. Not until treatment with several series of gonadogen was instituted were we able to obtain by biopsy, a secretory phase. In the sterility clinic at the Greenpoint Hospital, we were able to initiate with this hormone, the secretory phase in another patient with sterility who has had episodes of amenorrhea for three to six months, followed by anovulatory bleeding. Both of these patients have conceived.

I do not feel that this form of treatment in all cases of failure of ovulation is efficacious, for I must reiterate that there is in the human being, as well as in all other species, a specific organ response to hormones which may be refractory, and hence the patient may not respond to the administration of the hormone.

unit we observe a normal response as evidenced by corpora lutea of ovulation and estrus changes in the uterus. Larger doses produce tremendous enlargement of the ovaries with regressive changes in the follicles and corpora lutea atretica. Mature animals are much less regular in their response. The higher animals, such as the cat and dog, show greater variability. Hartman's work on monkeys demonstrates the difficulties of establishing a physiologic dosage, since refractory animals failed to respond to doses which produced overstimulation in others.

Similarly in the human being, the studies of Watson, Smith and Kurzrok demonstrate that with advancing age the ovary becomes refractory to gonadotropic substances. On the other hand, ovaries of high receptivity may respond to large doses with diffuse follicle development and marked ovarian enlargement. The total doses with which Kurzrok produced excessive ovarian enlargement were approximately five times as great as those reported here by Siegler.

Siegler's results, as well as those of Davis and Koff, would indicate that the total dosage for one menstrual cycle lies in the neighborhood of 60 units. Hartman's work on monkeys and Kurzrok's observations in the human being would suggest that reasonable caution should be used to avoid overdosage in susceptible individuals. Preliminary results with large doses in refractory individuals have not been encouraging.

I am glad that Siegler mentioned divided dosage. The single intravenous injection followed by laparotomy within twenty-four to forty-eight hours is a logical way to demonstrate ovulation. However, there is evidence both from animal and human experiments that, under some conditions, it may be desirable to distribute the total dosage over a sufficient time to permit the uterus to keep pace with the ovary. In applying this hormone to clinical practice the main problem is to choose a dosage and timing of injections which will induce as nearly as possible a normal physiologic response in both ovary and uterus. Siegler's data help to throw light on this important question.

Beilly has mentioned his observations on the instability of the mare serum hormone. I would like to ask Beilly if he is referring to the preparation in dry form such as gonadogen.

DR. BEILLY: I have not used the dried product but a solution of the hormone instead.

DR. CARTLAND.—During the past six years we have been studying the mare serum hormone both in solution and in the form of a dry powder. We have never been satisfied with a solution from the standpoint of stability. However, we are convinced that the dried product, as represented by the sterile vials of gonadogen used by Siegler, is reliably stable for more than a year. I believe this may be the answer to Beilly's observations on the questionable stability of the hormone in solution.

DR. ISIDOR C. RUBIN.—The matter of dosage remains still to be worked out, for the refractory elements which Siegler has referred to are factors which we do not understand. We cannot calculate for a single patient what the dosage should be. This point, by the way, holds true for practically all the hormone substances which have been elaborated in the last decade.

Of what ultimate practical use this hormone substance will be for the sterile patient cannot be stated at the present time. Davis and Koff, for example, reported 2 cases of pregnancy in a series of some 70 patients. Siegler mentioned one or two in his series. From the strictly scientific point of view we must be cautious in accepting such small percentage of pregnancies as proving the efficacy of a hormonal extract because of elements of chance. R. T. Frank has repeatedly called attention to the occurrence of such coincidental pregnancies in cases of amenorrhea which had no treatment at all, but were undergoing hormonal investigation.

It would also be desirable to have a series of patients with amenorrhea injected with this hormone. The pathology of the untreated ovaries in amenorrhea is now well known. If one could produce in such cases an appreciable number of fresh corpora lutea within 24, 48, or 72 hours, one would be convinced of the efficacy of this substance, since the ovaries associated with amenorrhea do not show active

This separation of pelves in three clinical groups should not be understood as being a dogmatic classification of pelves. It is, rather, an effort to give the clinician a point of view which loosely will include all of his obstetric patients. It undoubtedly oversimplifies the matter, but such dangers as may lie in this oversimplification may be met by qualifications which will vary somewhat according to the group into which a given patient is placed. The point of view demands the recognition of the adequate pelvis, of deviations from the adequate (handicaps), and of compensations. Fig. 1 is a schematic illustration of the three groups, in which the circle represents the pelvic inlet and the lines the birth canal below the inlet.

These diagrams (Fig. 1) represent the algebraic sum of handicaps and of compensations and are by no means intended to be diagrams of any particular pelvis.

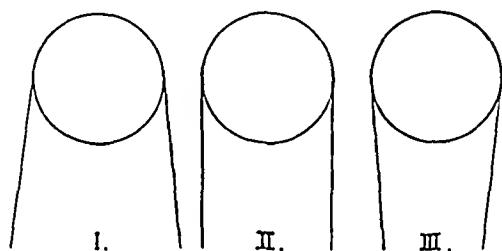


Fig. 1.

*An Adequate Pelvis.*—Gross deformities are not considered; in this country they are rare and may be dealt with as the occasion arises. The first criterion of an adequate pelvis is looked for in the true conjugate diameter. This is accurately read from the inlet roentgenogram, and is further checked from the lateral view. Litzmann's classic definition of a contracted pelvis gives 9.5 cm. as the true conjugate in the flat and 10 cm. for the generally contracted pelvis. Davidson<sup>2</sup> feels that a baby weighing 6.5 or 7 pounds may come through a pelvis with a C. V. of 8 cm. provided there is plenty of room in the transverse diameter. Bailey,<sup>1</sup> in a series of 221 generally contracted pelves, reported the spontaneous delivery of 9 whose estimated C. V. was only 8 cm. Peckman and Kuder<sup>10</sup> classified all pelves as contracted when the diagonal conjugate measured 11.5 (C. V. of 10 cm.) or less, regardless of other measurements.

No definite minimum for the C. V. diameter can be set. Important though it is, only one of the steps in the mechanism of labor, that of engagement, is concerned with the true conjugate. Nevertheless, this *relative* importance of the C. V. is vital in any estimation of labor prognosis. For the moment, it may be considered adequate if engagement into it is possible. From this point on the classification of the patient into one of the three groups depends upon the extent to which this adequacy is added to or subtracted from by the handicaps or compensations presented by the form and dimensions of the remainder of the birth canal. No attempt will, therefore, be made to judge the adequacy of the canal below the inlet except in relation to the inlet or to other important dimensions. The tendency for the failure of a given pelvis to conform throughout to any one pelvic type (gynecoid, android, etc.) has been shown by Caldwell, Moloy and D'Esopo<sup>12</sup> and renders it generally impossible to base a prognosis of labor upon any one dimension. Further consideration will, therefore, be upon the basis of handicaps and of compensations.

*Deviations From the Adequate Pelvis (Handicaps).*—The vital, though relative, importance of the C. V. has already been mentioned. The importance of this

## PELVIC PROGNOSIS ON THE BASIS OF RECENT X-RAY STUDIES OF THE FEMALE PELVIS\*

E. C. HARTLEY, M.D., ST. PAUL, MINN.

PROBABLY our understanding of pelvic contraction has advanced as far as is possible on the basis of external pelvimetry and either manual or instrumental internal examination. The roentgenologic study of the pelvis as introduced by Thoms, by Caldwell, Moloy and D'Esopo, and others, has given us accurate methods of measurement and conceptions of form which are universally comparable. Upon the basis of this work there is growing a better understanding of the obstetric pelvis.

We have, in all of this recent work, an implication which must be kept in mind in the study of the pelvis by whatever means, namely, that we make such a study, not primarily to classify it, but to make a prognosis of labor from it: Can we deliver, with safety to mother and child, through a given pelvis? It is the special virtue of recent roentgenologic studies of the pelvis that they give us a more accurate, more easily comparable and more complete basis for making such a prognosis.

Notwithstanding the improved understanding of the obstetric pelvis, there is as yet nothing in the nature of a "mathematical formula" for the prognosis of labor. There is, however, a tendency to anticipate a prognosis of labor with more assurance than was previously possible. This anticipation is more specific than was heretofore possible, in that it directs attention to definite "trouble spots" at which the presenting part may, on the one hand, be arrested by a narrowing of the canal, or on the other, be diverted in such a manner as to interfere with the normal mechanism of labor.

In the following group of patients, the recent work of Thoms and of Caldwell and Moloy, and others,<sup>3-5</sup> has been used to make a simple clinical classification designed to group patients according to prognosis. Within this grouping of patients, mistakes are still possible; it may, however, by forcing us at once into the ultimate purpose of pelvic study, aid us in agreeing more generally upon what is significant in pelvic form and dimension.

The classification includes three groups. A pelvis having an absolute contraction at the inlet is excluded. The three groups are as follows:

- I. Engagement being possible, labor will proceed with increasing ease.
- II. Engagement being possible, labor will proceed uniformly.
- III. Engagement being possible, labor will proceed with increasing difficulty.

\*Presented before the Chicago Gynecological Society, May 19, 1939.  
The roentgenograms in this group of patients were made by Mr. John S. Rose, of Dr. R. G. Allison's X-Ray Laboratories. Mr. Rose also set up the arrangement for using the Thoms grid in the lateral views.



Fig. 2.—Lateral erect position at 60 inch focal film distance. 100 K.V.P., 40 M.A., time 30 to 40 sec. Erect Bucky diaphragm. The central ray is directed to a point 2 inches behind and at the level of the anterior superior spines of the ilia. A cord is stretched taut at this level, attached to the tube stand and to the center of the Bucky tray. The patient is rotated until the anterior superior spines are at an equal distance from this cord. This assures a true lateral view.

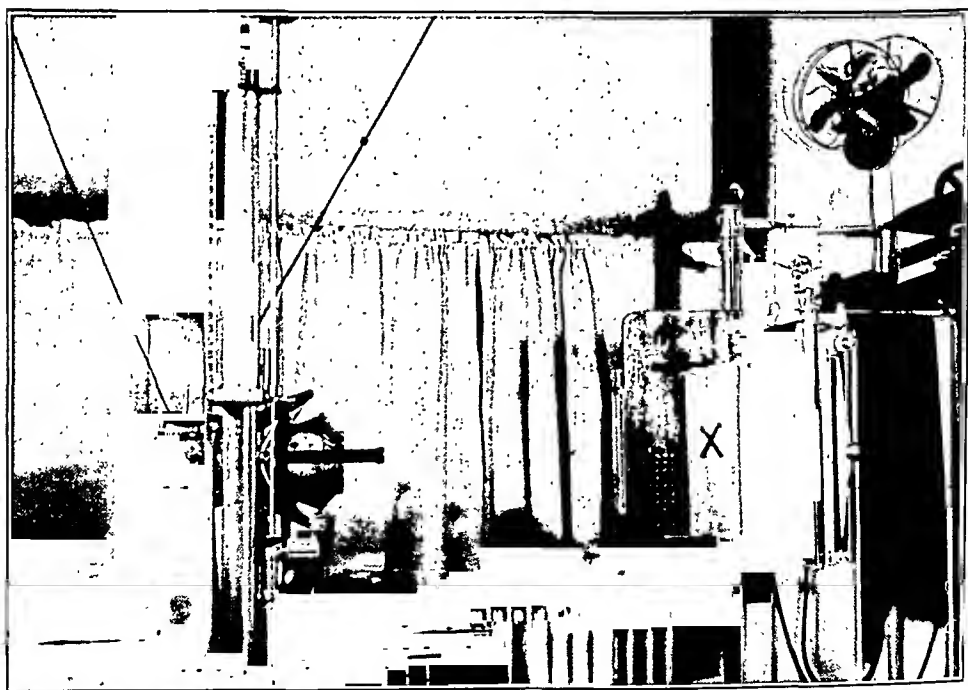


Fig. 3.—The 60 inch focal film distance minimizes distortion. The distance between the anterior superior spines is measured, after the exposure is made, and a mark is placed midway. Then the distance from this mark to the Bucky is measured and the Thoms plate or grid "X" placed at this point, as shown in Fig. 2, for the fractional second exposure, which produces the dots on the film.

measurement, even at the inlet, is not absolute, but must, in most instances, be judged also in relation to inlet shape. For example, a C. V. of 11 cm. in a gynecoid pelvis which runs true to type throughout will offer no problem; even an android type with such a C. V. will often present no particular difficulty. There is this difference, however: the capacity of the fore pelvis in the android type is limited, and it will tolerate with safety less outlet or sacral handicaps than will the gynecoid.

The handicap of converging sidewalls or of a converging lateral bore is important, but, as with the C. V., this importance is relative. It is conceivable that a favorable prognosis might on occasion be given to a patient in Group III, since the inlet may have been sufficiently large to provide ample leeway for some degree of narrowing.

The importance of the biischial measurement has been recognized since Williams showed its importance as a factor in dystocia and as a criterion for the diagnosis of the funnel type of pelvis. This measurement, as it diminishes under 8 cm., becomes increasingly a handicap. Again, however, its importance is relative and must be judged, as Williams showed, in connection with the posterior sagittal diameter. It must also be judged, as shown by Caldwell, Moloy and D'Esopo,<sup>7</sup> and by Schuman,<sup>6</sup> in relation to the level of the sacral shelf and to the depth of the pelvis. Caldwell and Moloy found a narrow subpubic angle associated with a narrow forepelvis in 60 per cent of their cases, while wide arches showed narrow forepelves in 42 per cent. They did find, however, that narrow arches were associated with converging sidewalls in 100 per cent of the cases studied.

A high sacral shelf may become a serious handicap, all the more so since it is easily missed. Caldwell, Moloy and D'Esopo<sup>7</sup> discuss the lower sacral segment at length, particularly in relation to its level as effecting extension of the fetal head at a point to coincide most advantageously with the opening beneath the pubic arch. They feel that the proper coincidence of the movement of extension from its take-off, so to speak, to its termination under the pubic arch is not solely a matter of suitable relationship between the two linear dimensions of bituberous and posterior sagittal, but of the level from which this important factor in the mechanism of labor starts.

#### PROCEDURE

The level and configuration of the lower sacral segment is well revealed in the lateral roentgenograms. In viewing the lateral roentgenograms, the use of a simple device is of help in quickly visualizing the level of the sacral shelf in relation to the pubic arch and the depth of the posterior pelvis. It consists of a transparent piece of stiff celluloid material ruled off in centimeter squares. The material is large enough to cover all diameters of the pelvis in the lateral view. In using it, the edge is placed so as to lie along the plane of the inlet. Such factors as the relation of the sacral tip to the ischial spines, and the posterior sagittal diameters at various levels in the pelvis may be readily visualized and measured.

*Compensations.*—As the term implies, compensations are favorable combinations of dimensions or form which tend to overcome handicaps. Thus, an inlet of ample dimensions may well compensate for some degree of convergence in the sidewalls or lateral bore. On the other hand, an inlet borderline in size will cause less concern if it is associated with parallel or divergent sidewalls and lateral bore; the same is true with an android type of inlet.

A wide bituberous diameter tends to compensate for a high sacral shelf; a shallow pelvis will also help greatly in this connection.

Wide lateral dimensions at the inlet tend to compensate for diminished measurements in the C. V. With such a flat type of pelvis, however, as has been pointed out by Caldwell and Moloy, there must be ample space low in the pelvis for the rotation of the head from the transverse (in which position descent has taken place) to the anteroposterior, so that extension may take place. Such space is given by a wide arch, a shallow pelvis, and a lower sacral segment giving ample posterior sagittal dimensions.



## CONCLUSIONS

In the absence of a "formula" upon which to base a prognosis of labor, the approach above described has been found useful as a tentative means of using the findings of recent x-ray studies clinically. Beginning with the form and dimensions of the inlet as a point of departure, or base, the progress of labor from that point on is pictured as falling into one of three possible groups. The criteria which place a given pelvis into one particular group are found in varying combinations of form and dimension in the sidewalls and lateral bore, the lower sacral segment, pelvic depth, and the bituberous diameter at the outlet. These criteria are variables within any classification of pelvises and, hence, for each individual pelvis, must be checked against each other as a series of handicaps or compensations whose algebraic sum gives us our prognosis.

## SUMMARY

1. A method of classifying pelvises according to expected prognosis of labor is presented. The classification is based upon recent advances in pelvic roentgenography of Thoms, of Caldwell and Moloy, and others.

2. The use of Thoms' grid in lateral views of the pelvis is discussed.

3. A simple device to aid in visualizing certain relationships in the lateral roentgenograms is described.

4. A series of cases is presented with an analysis of several on the suggested prognostic basis.

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## DISCUSSION

DR. WILLIAM B. SERBIN.—The classical contributions to our knowledge of the obstetric pelvis, more especially with reference to the classifications of Michaelis, Litzmann, Schauta, and Breus and Kolisko, are gradually being supplanted by the recent and more accurate observations of Caldwell and Moloy and Thoms. Whereas, the observations of these obstetricians could only be limited to a study of dry pelvises and crude measurements in the living, the modern investigator has had the advantage of refined x-ray technique. Even x-ray has had to undergo various stages of experimentation from the original simple plate to the present opportunity of almost perfect measurements by the screen grid technique of Thoms or the stereoroentgenoscopic method of Caldwell and Moloy.

The factor of the size of the fetus is obviously important but can only be discussed very briefly at this point. The size of the fetus in relation to the adequacy of the pelvis may be judged in several ways: (1) Within limits the fetus is extremely adjustable as to postural adaptation and within limits it is compressible. (2) The weight of a fetus may with experience and in an abdomen which lends itself readily to palpation be judged with considerable accuracy. (3) Various maneuvers may be carried out to determine whether or not the fetal head will enter the inlet. (4) Lateral pelvic roentgenograms will indicate the level to which the fetal head may descend into the pelvis.

The factor of forces of labor is also important. Labor pains to be effective must be strong and frequent. Their strength and effectiveness must be determined by abdominal palpation and not be interpreted from the subjective symptoms of the patient. Chemical imbalances in the blood serum of patients may occasionally seriously alter the effectiveness of the uterine contractions.

Improvement in infant mortality rates has been steady over a number of years. The decline in rate has been conspicuous in the gastrointestinal group of diseases, the contagious diseases and the respiratory group; least of all has it been observed in the neonatal group. In this group, which now include 52.2 per cent (1936),<sup>9</sup> of the infants dying annually in the registration area, are the premature deaths, the birth injuries, the congenital malformations, and a number ascribed to other causes associated with the natal and prenatal period. Peekman and Kuder,<sup>10</sup> reporting on 422 cases of "borderline" contracted pelves delivered by the vaginal route, report a gross infant mortality of 19.23 per cent. They say, "Our experience indicates that the risk to the child is markedly increased in prolonged labor through a contracted pelvis." Thoms,<sup>11</sup> commenting on the effect upon the fetus of difficult vaginal delivery, says, "The toll of fetal deaths in such operations has received in the past too little attention." Further lowering in the present infant mortality rates must come, at least in part, through early recognition of pelvic contraction in pregnant women, and their eventual delivery planned with the type, location, and degree of this contraction in mind.

Limitations in such studies as this of pelvic form and dimensions should be kept in mind. What they represent is a part only of an anticipated plan of delivery for a specific patient. The plan necessarily has other parts, but only so far as each part becomes more and more accurate can we hope for improvement in our complete care of the obstetric patient.

The 51 cases studied in this report classified according to Thoms and to Caldwell and Moloy's method are as shown in Table I.

TABLE I

THOMS' CLASSIFICATION	THIS SERIES 51 PRI. PTS.	THOMS' SERIES <sup>4</sup>		686 TOTAL
		582 CLINIC	104 NURSES	
Dolichopellic	11.7%	15.0%	37.5%	18.4%
Mesatipellic	53.0	44.8	44.2	44.7
Brachypellic I	27.3	25.0	12.5	23.1
Brachypellic II	4.0	9.3	5.7	8.7
Platypellic	4.0	5.6	—	4.7
CALDWELL-MOLOY METHOD	THIS SERIES 51 PRI. PTS.	PETTIT, ET AL. 100 PRIM.	CALDWELL, MOLOY AND SWENDSON <sup>12</sup>	
Gynecoid	55.0%	51.0%	50.6%	
Android	27.5	21.0	22.4	
Anthropoid	11.7	18.0	22.7	
Platypelloid	5.8	5.0	4.4	
Asymmetrical	—	5.0	1.8	

TABLE I. THE OBSTETRIC ASPECTS OF ALL REPORTED CASES OF STREPTOCOCCUS VIRIDANS ENDOCARDITIS IN PREGNANCY

AUTHOR	AGE	PARA	PAST HEART HISTORY	ONSET OF SYMPTOMS	TIME OF DELIVERY	TIME OF DEATH POST PARTUM	PREGNANCY TERMINATED BY	STR. VIRIDANS RECOVERED IN	FETUS
Freund <sup>1</sup> (1913)	30	ii	Rheumatic heart disease	1 month	Undelivered	Ante partum	Undelivered	Heart blood at autopsy	Nonviable
Findley <sup>2</sup> (1921)	30	ii	Not stated	"Early"	4 months	3 weeks	Vaginal hysterotomy	Maternal blood	Nonviable
Walsers <sup>3</sup> (1928)	23	i	Chorea and rheumatic fever	6 months	8½ months	1 month	Spont. labor and delivery	Maternal blood and Fetal blood	Culture neg. in 1 week
Walsers <sup>3</sup> (1928)	24	0	Not stated	6 months	7½ months	"Several months"	Spont. labor and delivery	Maternal blood and Fetal blood	Died after 17 hr. (Wt. 1700 gm.)
Kobacker <sup>4</sup> (1930)	18	0	Rheumatic heart disease	3 months	9 months	4 days	Cesarean section (on moribund patient)	Maternal blood and Fetal blood	Culture neg. in 2 weeks
Reids <sup>5</sup> (1930)	?	v	Rheumatic heart disease	?	5 months	5 months	Spont. abortion	Maternal blood	Nonviable
Mengert <sup>6</sup> (1933)	21	0	Rheumatism "Dyspnea and edema"	6 months	8 months	6 months	Spont. labor, breech delivery	Maternal blood	Living
Mengert <sup>6</sup> (1933)	27	iv	Negative	8 months	9 months	7 weeks	Spont. labor, breech delivery	Maternal blood	Living
Terwilliger <sup>7</sup> (1934)	21	i	Negative	7½ months	8½ months	Not stated	Spont. labor and delivery	Maternal blood and urine	Living. Negative cultures

I agree, therefore, with the essayist's opening statement that "our understanding of pelvic contraction has advanced as far as is possible on the basis of external pelvimetry and either manual or instrumental internal examination."

Dr. Hartley now proposes to make a prognosis by means of pelvic roentgenometry. His criteria are measurement of the conjugata vera, depth of pelvis, character of lateral pelvic walls and pubic arch, and contour of the sacrum, etc.

Exclusive of extreme contraction, three types are recognized, based on engagement: (1) Labor proceeding with increasing ease; (2) labor proceeding with uniformity; (3) labor proceeding with increasing difficulty. This classification is desirable because it attempts a prognosis upon our borderline cases. While his series is admittedly small, his analysis has been meticulously worked out.

Many of you would like to know the feasibility of routine x-ray during pregnancy or labor. True, special apparatus and special technique are necessary; the method requires two views, and finally it is expensive. When we bear in mind that 85 per cent or more patients have normal or nearly normal deliveries, it is obvious that x-ray pelvimetry is not necessary in this group. The remaining 15 per cent, and these give some evidence beforehand, viz., contraction of inlet, convergent pelvic walls, decreased lateral bore, narrow arch, "shelving of sacrum," some such method is highly desirable. X-ray pelvimetry does not and should never supplant clinical judgment.

Dr. Hartley should collect a larger series, and give the Caldwell and Moloy and Thoms' classifications and their revisions of the mechanism of labor a more severe test.

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## THE TREATMENT OF AFTERPAINS AND PAINFUL ENGORGEMENT IN THE PUERPERIUM WITH TESTOSTERONE PROPIONATE

### A PRELIMINARY REPORT

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AMONG the most common and distressing complaints of the puerperium are afterpains in multiparas, and painful engorgement of the breasts, usually in primiparas. This report presents our experiences with the use of the so-called male sex hormone, testosterone propionate, in the relief of these conditions.

Briefly stated the therapeutic rationale for the use of testosterone propionate is as follows: All the sexual hormones are definitely bisexual in their action, though to a varying degree.<sup>1</sup> Embryologically,<sup>2</sup> as well as biologically,<sup>3</sup> the female gonad exhibits strong bi-sexual potentialities. Normal human females excrete from one-sixth to as much androgenic substances in their urine as do normal men.<sup>4, 5</sup> Testosterone is not only strongly androgenic, but it is also a very potent gynecogen, especially as regards its stimulative action on the female genital tract.<sup>1</sup> Its action is dual, however, in that it resembles estrogens in many respects,<sup>6</sup> yet on the other hand it may simulate the action of progesterone.<sup>7-9</sup>

Testosterone will inhibit rhythmic, intermittent contractility of the uterus as well as desensitize it to the action of pituitrin.<sup>8, 9</sup> The exact action of testosterone on the human breast is not yet known.<sup>10</sup> Therefore its use in mastalgias is purely empirical.

Clinically, we have found that testosterone propionate will relieve dysmenorrhea.<sup>11</sup> In addition, it was noted that premenstrual breast tension was also relieved.

Proceeding on this experimental and clinical evidence, we began to treat afterpains and painful engorgement of the breast in the puerperium with testosterone propionate.

## I. AFTERPAINS

The etiology of this condition is not known. However, most observers seem to agree that relatively excessive contractions seem to be the immediate cause of the pain,<sup>12</sup> probably resulting from a transient local ischemia.<sup>13</sup>

First it was decided to employ testosterone propionate (t.p.) to prevent afterpains. For this purpose 100 multiparas (almost all private patients) were chosen, 75 serving as controls. Both groups were similar in average age, parity, and duration of labor. Analgesia and anesthesia were also similar. Each group received a course of 6 doses of ergonovine, gr. 1/320, during the first two days of the puerperium. The test group received 10 mg. of testosterone propionate by deep subcutaneous injection in the deltoid region, fifteen minutes to two hours after the third stage of labor.

In the control group of 75, 24 per cent (18) had little or no discomfort, 56 per cent (42) received marked to moderate relief with two to four doses of codeine (gr. i) or ten doses of acetylsalicylic acid (gr. x. q. 4 h.), while 20 per cent (15) required several doses of codeine over a period of thirty-six to seventy-two hours.

In the test group, 88 per cent (22) had no pain at all or an occasional vague pain, usually after an ergonovine tablet, which required no analgesia. Of the three who failed to get relief, one received complete relief with an additional 5 mg. of testosterone propionate ten hours later, one received marked relief with an additional injection of 5 mg. of testosterone propionate twelve hours later, and the third one failed to get relief with 30 mg. of testosterone propionate.

Forty-nine patients with severe afterpains, many of whom had failed to respond to ordinary analgesia, were treated in the following way: Five milligrams of testosterone were given intramuscularly and one hour later 5 mg. more subcutaneously in order to sustain the initial reaction over a longer period of time. In some cases 10 mg., divided between the two routes, were given at one time. Relief was usually apparent in from twenty minutes to an hour. Therapy was successful in rendering adequate relief in 82 per cent (41) of the patients treated. Of the remaining 8, 2 secured complete relief with an additional 5 mg. Six (13 per cent) received little or no relief, even with 20 mg. in two cases, and 15 mg. in 3 cases.

No effect on lochia or on lactation was noted. It was the general impression that involution of the uterus was definitely hastened, but unfortunately this observation was noted too late for statistical study.

No correlation could be made between the occurrence of afterpains and a previous history of dysmenorrhea.

## II. PAINFUL ENGORGEMENT

Engorgement of the breasts usually begins thirty-six to seventy-two hours after delivery and may become very painful six to twenty-four hours later, lasting from six hours to three days. Engorgement is much more likely to be painful in primiparas, in those who do not nurse, in those whose babies nurse poorly, or in those who wean their babies for one reason or another. Pain is much more likely to occur where the breasts are small. The pain may be centered about the nipple or be situated at the upper, outer quadrant of the breast.

Fifty cases of severe painful engorgement of the breasts were treated with testosterone propionate. Many of these had failed to receive relief with an adequate tight uplift binder, ice caps, and analgesics.

Treatment consisted in stopping previous medication, and giving 5 mg. of testosterone intramuscularly and another 5 mg. subcutaneously an hour later. Relief was usually apparent in one-half to one hour and was practically complete in three to six hours. Occasionally a mild transient galactorrhea was noted. The breasts generally became completely soft in three days, if the baby did not continue to nurse. In mothers who continued to nurse their babies, no inhibition of lactation was noted. This was checked by weighings. No ill effects of any sort were evident in the babies.



Fig. 1.—Anteroposterior roentgenogram from Case 1, from which the diagnosis of hydrocephalus was erroneously made. Note the absence of characteristics of hydrocephalus and the tendency toward occipital flattening. Tube-film distance of 30 inches employed.

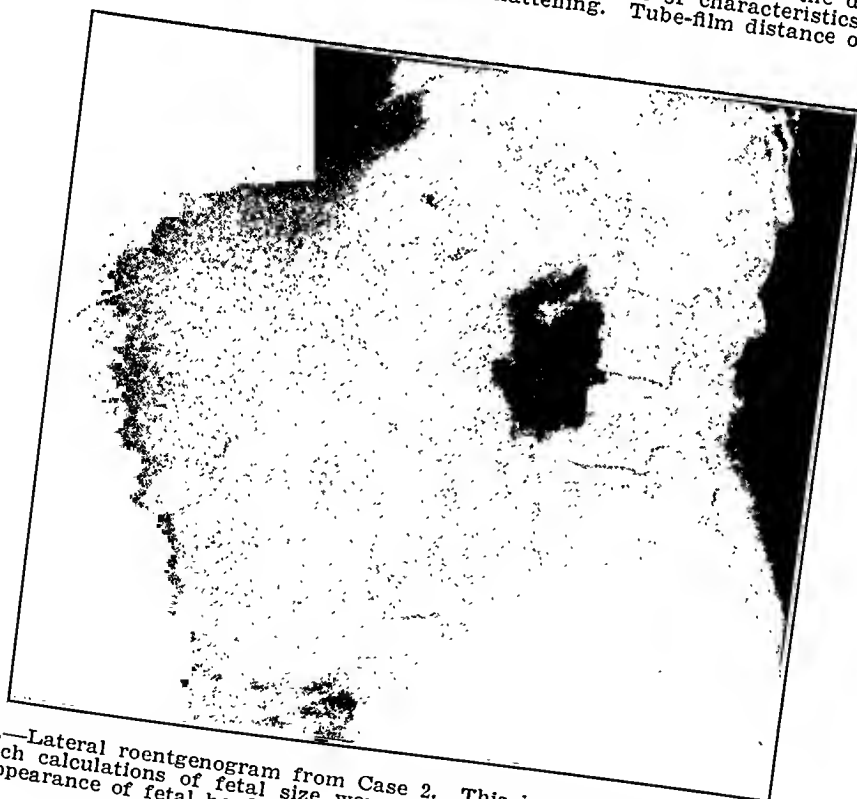


Fig. 2.—Lateral roentgenogram from Case 2. This is one of the stereoscopic films from which calculations of fetal size were made by the Hodges method. Note the normal appearance of fetal head size and shape. Tube-film distance of 36 inches employed.

Fig. 2; this is reproduced, rather than an anteroposterior one, since in the latter an oblique view of the fetal head was obtained. From the stereoscopic films a diagnosis of a normally formed fetus was made, and the resulting uncorrected figures for fetal head size are recorded in Table II. Because of the funnel pelvis and breech position, an elective cesarean section was performed on October 31, and a normal male child, weighing 7 pounds (3,175 gm.), was delivered in good condition. Measurements obtained soon after birth appear in Table II.

#### DISCUSSION

A comparison of some of the above figures will reveal that simple divergence of x-rays can account for an exaggeration of fetal head shadow amounting to more than 50 per cent when the fetal head lies in the fundus and is viewed from the anteroposterior position. This large amount of distortion is due to the fact that when the fetus presents by the breech, its head lies at a greater distance from the film than when the fetus lies in an occipital position; in cases of the latter position the distortion rarely amounts to as much as 25 per cent. The added increase in distortion of the fetal head when it lies in the fundus, may be avoided by obtaining the roentgenogram with the patient in the lateral position, for in this position the fetal head will gravitate to a lower level and will approach the film more closely than it possibly could with the patient lying on her back.

Furthermore, if one will view in a stereoscope the films of a fetal head that is suspected of being hydrocephalic, the size will be much less exaggerated than when viewed on a simple flat plate, and this is particularly true when some type of precision stereoscope is employed. Today, however, the use of any of the accepted methods of cephalometry (such as: Thoms,<sup>2</sup> Walton,<sup>3</sup> Ball,<sup>4</sup> Hodges,<sup>1</sup> Clifford,<sup>5</sup> or Johnson<sup>6</sup>), should avoid the possibility of erroneous diagnoses of intrauterine hydrocephalus made solely on the basis of exaggerated fetal head size.

Roentgenologists recognize several distinguishing characteristics of intrauterine hydrocephalus, and these should always be sought for when the fetal head appears, in any roentgenogram, to be unusually large. Among these are: the relatively small facial features, gaping sutures and fontanels, disproportionately small body and the globular shape of the fetal head. A normally developed fetal head rarely shows any tendency toward a globular shape when lying in the fundus. On the contrary, there is usually the suggestion of flattening of the occiput and this is best seen in Fig. 1 and was noted after delivery in the fetuses of both cases here reported.

The x-ray diagnosis of intrauterine hydrocephalus with the fetus in breech position should never rest on the apparent size of the head in a flat anteroposterior plate, but should be based only upon one of the other characteristics enumerated above.

#### CONCLUSIONS

1. The diagnosis of intrauterine hydrocephalus from flat anteroposterior roentgenograms when the fetus presents by the breech is hazardous.

2. Flat lateral roentgenograms or stereoscopic films will aid in avoiding an erroneous interpretation.

3. Cephalometry by any recognized position or stereoscopic method will reveal the true size of the fetal head.

4. An enormous fetal head shadow must include at least one of the characteristic features of hydrocephalus before such a diagnosis can be safely made.

5. To the usually accepted roentgenographic characteristics of intrauterine hydrocephalus, we should like to add: (a) the absence of occipital flattening in cases of breech position; and (b) the marked decrease in density of the vault of the skull, as observed by haziness of the fetal head shadow in this region, when compared with that of the base of the skull.

We wish to thank Dr. Louis H. Douglass, Chief of Division of Obstetrics at Baltimore City Hospitals, for the privilege of reporting Case 1; and Dr. Alan F. Gutmacher, Associate Professor of Obstetrics, Johns Hopkins University and Hospital, for allowing us to include Case 2.

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## IRRADIATION OF CANCER OF THE CERVIX

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THE end results of 158 cases of carcinoma of the uterine cervix treated with roentgen rays and radium in the Radiation Therapy Service at Bellevue Hospital from 1925 to 1930 were reported by Kaplan<sup>1</sup> in 1932. This presentation is a continuation of that series with a report of 677 patients observed during the period 1925 to 1937. In all but 3 of these the diagnosis was confirmed by sections examined by the pathologist to the hospital.

#### THE TYPE OF MATERIAL AT BELLEVUE HOSPITAL

In 232 patients the disease was so far advanced at the time of their admission that they had to be transferred to the City Cancer Institute for custodial care. The remaining 445 patients were treated in Bellevue Hospital, and of these 263 had either unilateral or bilateral parametrial involvement and 136 received only partial treatment. The type and immediate disposition of this group of cases is shown in Table I.

In this series of Bellevue Hospital cases we include 396 patients who had had no treatment for their malignancy prior to admission to the service, 16 patients who had had a previous hysterectomy and 33 who had x-ray or x-ray with radium therapy elsewhere and were then referred to our service for radiation therapy, either as a prophylactic procedure or for treatment of an evident recurrence.



TABLE I

Patients transferred to City Cancer Institute	232
Patients who had hysterectomy before admission	16
Patients treated by radiation before admission	33
Patients in whom treatment was begun but not completed at Bellevue	136
Patients who had complete therapy at Bellevue	260
Total	677

## EXTENT OF DISEASE

This study has been undertaken without grouping the patients, because it was felt at the time that the clinical classification of cancer of the cervix depended so much on individual interpretation as to be of little value. The method for classifying the types of cancer of the cervix now being attempted at Bellevue Hospital is based on the anatomic classification adopted by the Cancer Committee of the League of Nations.

We rarely see a patient with a cervical cancer before the ulceration and infiltration have extended into the involved deeper cervical tissues. Until the past four or five years, in fact, no cases could be placed in Group I, while a great number were in Group IV.

## SYMPTOMS

When admitted to the service the most frequent symptoms of which the patients complained were metrorrhagia, pain in the lower quadrants of the abdomen, irregular menses with intermittent spotting, and irregular prolonged periods. Clinic patients usually do not keep careful records of their menstrual cycle, but increased frequency of the menstrual period is the most common change that influences a woman to seek a doctor's advice. The severity of the hemorrhage does not, in all instances, indicate the extent of the disease, nor does a long history of symptoms necessarily mean that the case is hopeless.

Pain is usually present in patients with secondary inflammatory adnexal or broad ligament involvement; in no instance was pain present when the growth was localized in the cervix. Invasion of the rectum and of the bladder produces characteristic symptoms, while lateral invasion may result in pressure on the nerve trunks with pain radiating to the lower extremities. In other instances pressure over the lymphatics and veins causes swelling of one or both extremities.

## ROUTINE THERAPY

In the treatment of carcinoma of the cervix, neither x-rays nor radium should be employed alone. Patients, we observed, who had had an incomplete course of therapy either in our clinic or in some other hospital, did not have a favorable outcome. The roentgen ray treatment in the Bellevue clinic is usually started as soon as diagnosis is established. This therapy is followed by radium and later by a second course of x-ray.

*Diagnosis.*—In addition to the routine palpation and inspection of the cervix, digital rectal examination is always done to determine the condition of the parametria and lymph nodes located at the bony pelvis. At times proctoscopic examination of the lower sigmoid and rectum is performed to discover possible extension of the disease to these parts. Routine cystoscopic examination is highly advisable, and for several months we have established this procedure as a routine measure. In quite a few patients occlusion of a ureter was found as the result of invasion of the ureteral walls or from pressure of involved adjacent lymph nodes.

1. *Preradium X-ray.*—As soon as diagnosis is established, x-ray therapy is commenced. Until 1929 the technique of irradiation as employed by us was one skin erythema dose to each of four areas of the lower pelvis, anterior right and left, and posterior right and left, one-quarter dose administered over two areas daily. Since 1929, higher doses were delivered and a larger number of areas were treated; namely, two anterior and two posterior lower pelvic areas, two lateral to affect parametrial involvement and in cases with bulky cervical masses, vulva and anal areas were added. The dose administered was 1,200 to 2,400 r. to each portal. To

the vulva and anal areas, however, only 900 to 1,000 r. were given, as severe epidermitis develops after this amount of irradiation.

2. *Radium*.—Vaginal application of radium follows the completion of the preliminary course of roentgenotherapy. Radium, in a rubber sound, is inserted into the uterine canal and a colpostat with two or three corks is placed against the cervix, and held in place with several pieces of iodoform gauze packing. The radium is filtered through 1.5 mm. platinum in the sound and 2.5 mm. platinum in the colpostat. The radium applicators remain in situ for 96 to 120 hours. After the radium is removed, the patient is discharged in one or two days if no untoward effect has occurred. She returns for observation every two weeks thereafter.

Upon completion of this series, radium was applied using a sound in the uterine canal and a colpostat with two or three corks against the cervix, held in place with iodoform gauze packing, and a total dose of 5,000 to 7,000 mc. hr. administered.

3. *Postadium X-ray*.—Since 1929, an additional course of x-ray, following the radium, has been given. With the use of the saturation method, as suggested by Pfahler, higher doses can be delivered without damage to the skin. This method is employed by us in order to deliver the maximum amount of irradiation to the tumor bearing area. In many instances of very advanced cases in which the treatment was given as a palliative measure, healing of ulceration with cessation of bleeding and discharge has followed with improvement in the general health of the patient.

The postadium course of x-ray therapy is given at the end of two months, or as soon as the radium membrane on the vaginal mucosa has disappeared. It is directed as a rule through four portals, but in advanced cases with residual parametrial involvement, two lateral portals are added. The dose administered was 1,200, 1,800, or 2,400 r/u to each portal. The factors used were 200 kilovolts, 8 to 20 milliamperes, 40 to 50 cm. target distance, and filters of 0.5 mm. copper plus 1.0 mm. aluminum, administered at the rate of 16 to 50 r/u per minute.

*Complications*.—In some patients x-ray treatment had to be terminated prematurely when the skin reaction reached a third degree epidermitis, or actual blistering of the skin. Daily applications of aquaphor ointment were very helpful. Changes in the mucosa of the vaginal wall were rarely observed, even when the vulval and anal areas were treated. This was due to the comparatively small dose applied to these regions, and because the amount of irradiation reaching the vaginal wall from the pelvic areas was too small to cause changes in the mucous membrane.

While the protracted irradiation was being administered, vaginal and bowel hygiene were carefully observed, and the general condition of the patient was improved by means of proper diet and transfusion when necessary.

Bladder irritability, except for a transient frequency of urination, was unusual. Intestinal disturbances were more constant and were manifested by diarrhea and cramps lasting several days, in a few cases only did it last longer and cause prostration and loss of weight. These symptoms are usually combated by hospitalization and such supportive measures as transfusions and infusions of saline, and glucose were indicated only after the following routine procedures failed to control the symptoms.

1. Citrous fruit juices are given routinely after each treatment to control acidosis.
2. Bicarbonate of soda will sometimes relieve the symptoms.
3. Calcium gluconate before meals in 15 gr. doses.
4. Liver extract per os or intramuscularly.
5. Vitamin B per os or intramuscularly.
6. Nembutal or other sedatives.
7. Adrenalin 1:1000, 3 or 4 min. per os 5 minutes before starting treatment.
8. Friedman's mask.
9. Ice cold ginger ale.
10. Rectal taps may be necessary and one may even have to resort to hypodermoclysis in certain instances.

Pelvic infection was a more serious but rarer complication. The most important aspect of this problem is the prevention of infection. Especially to be feared is latent gonorrheal involvement of the adnexa which may be lighted up by radiation.

In all cases immediate removal of the radium is indicated if the temperature rises to 103° F. or more, the treatment being completed only after the infection subsides. Later pyometra is avoided by promoting adequate drainage from the uterine canal by frequent insertion of a sound in the canal to prevent its occlusion by adhesions. If the radium is re-applied in such cases a modified procedure is used. Dilatation and reposition of the radium in the uterocervical canal is avoided for fear of another flare-up of the pelvis infection. Radium needles are sometimes inserted in such a way as to surround the uterine cervix, and the colpostat is replaced as originally. The postadium course of x-ray therapy in these cases is more intensive, in order to affect residual malignancy.

#### SPECIAL TYPES OF TREATMENT FOR UNUSUAL SITES OF GROWTH

In a few patients where the recurrence was located on the lateral vaginal wall a mold or a special applicator with radium tubes was constructed and placed against the involved area, thus providing direct contact irradiation to the lesion. The other parts of the vagina are protected by a lead shield and gauze packing.

In patients where the rectovaginal wall was involved a specially constructed proctostat bearing a number of radium tubes was placed in the rectum and an applicator placed in the vagina, thus providing crossfire irradiation to the involved area.

In malignant infiltration of the anterior vaginal wall a specially constructed applicator was inserted into the vagina, in contact with the lesion.

In some patients with a bulky tumor mass formation radium needles were inserted parallel to the urethra. A retention catheter was always used in these patients.

In one case a histologically proved metastasis to the tibia occurred three and one-half years after irradiation.<sup>11</sup>

#### END RESULTS

In evaluating the results from treatment of cancer of the cervix, it has been generally accepted that a patient who is alive and free from clinical evidence of the disease five years or more after treatment is a successful case. For this reason the results in only 276 malignant cases seen and treated during the period from 1925 to 1933 are discussed.

TABLE II. END RESULTS

	TOTAL	NO. DEAD	CONDITION AT LAST VISIT		NO. ALIVE AND WELL AT 5 YR.	PER CENT ALIVE AND WELL AT 5 YR.
			WELL	POOR		
Total number of cases seen in <i>Bellevue Hospital</i>	396				46	9.3
Exclusion of 120 cases transferred to City Cancer Institute <i>Patients treated in Bellevue Hospital</i>	276	130	36	64	46	16.6
Omitting 23 patients radiated previously elsewhere <i>Primary Bellevue Cases</i>	253	118	34	57	44	18.2
Omitting 9 patients operated upon previously elsewhere <i>Primary Bellevue Cases</i>	244	112	33	55	43	18.6
Omitting 107 patients in which therapy was not completed <i>Bellevue Patients Completely Treated</i>	137	112	33	55	43	33.1

The charted results shown in Table II reveal the fact that the total number of patients known to be alive five years or more was 46. When all cases are included, then the five-year salvage rate is 16.6 per cent, but if deduction is made of the 23 patients who were treated elsewhere with radium or x-rays, of the 9 patients who had a hysterectomy prior to admission to our service, and of the 107 who never returned to complete their course of therapy, then the five-year salvage rate rises to 33.1 per cent. Of the excluded cases, two that were treated elsewhere and one following hysterectomy are alive five or more years following therapy in our clinic.

Table II illustrates the special problems faced by a city hospital cancer clinic in the treatment of cases and in the accurate presentation of end results in a form comparable with those of the private institutions which receive principally primary cases. It shows also how the actual figure to be reported for the absolute cure rate will vary from 9 to 33 per cent, depending on the initial acceptance or rejection of certain groups of hopeless cases from the tabulations.

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#### LATENT GONORRHEA IN OBSTETRIC PATIENTS

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THE gonococcus has long been identified as an etiologic factor in puerperal morbidity and the syndrome of second-week fever associated with lower abdominal pain and considerable general reaction has been recognized as characteristic of this type of puerperal infection. It has also been appreciated that certain women who harbor gonococci even during the last month of pregnancy suffer no such complication, but the true extent of such silent infections could not be demonstrated. Recently improved cultural techniques offer the opportunity to approximate more closely the true frequency of latent gonorrheal infections. This report is concerned with an investigation by modern bacteriologic methods of the vaginal flora of a consecutive series of patients admitted to the University Hospitals for delivery.

#### MATERIAL

The series included 500 unselected women admitted in the last two months of gestation for delivery and post-partum care. Among this group, 431 (86.2 per cent) were married, while 69 (13.8 per cent) were single (50), divorced (8), separated

(9), or widowed (2). Two hundred and thirty-three (46.6 per cent) were pregnant for the first time, and the remaining 267 had had from 1 to 14 previous children (average, four plus), and 83 gave histories of previous miscarriages.

### TECHNIQUES

At the admission ante-partum examination, usually within twenty-four hours after entrance, the cervix was exposed through a sterile speculum. Swab cultures were taken from the canal and from the posterior vaginal fornix for: (a) gonococci, (b) monilia, and (c) trichomonads, and treated as described below. Spreads were made from both areas on clean microscopic slides. Blood was drawn for the gonococcus complement fixation test as well as for the serologic tests for syphilis. A search was made for stigmas of gonorrhea and a careful history was taken to elicit evidence of previous gonococcal infection. This portion of the study was carried out by one individual (W. W. T.) who also examined the stained spreads.

*Identification of Gonococci.*—Following the recommendations of Carpenter,<sup>1</sup> one swab from each area was placed immediately in Douglas broth (1.0 c.c.) and transported to the laboratory where it was rubbed over the surface of a chocolate-agar plate (Douglas agar with 5 per cent sheep's blood). One drop of the Douglas broth suspension was also pipetted onto the surface of a second chocolate-agar plate and spread uniformly over the medium with a sterile glass spatula. Thus, two plates were inoculated with material from the cervix and two from the posterior vaginal fornix. (Isolation of the gonococcus was readily achieved from the first plate when the flora was scanty, but was more easily carried out from the second plate when the bacterial growth was plentiful and mixed.)

The inoculated plates were sealed and incubated for forty-eight hours at 37° C. in special jars in which the carbon dioxide content was increased to approximately 12 per cent. At the end of this period the plates were examined for typical colonies.\*

If none was seen, the surface of the agar was flushed with a few drops of a 1 per cent aqueous solution of dimethyl paraphenylene diamine hydrochloride† which within a few seconds turns gonococcus colonies red and later black. The organisms can be successfully subcultured while the colonies are red but die during the development of the black discoloration. This color reaction is known as the "oxydase test" and organisms which react are "oxydase positive."

All "oxydase positive" colonies were subcultured on chocolate-agar plates. After incubation for forty-eight hours, smears were made and stained by the Gram method. When examination revealed gram-negative diplococci, pure cultures of these organisms were obtained and inoculated onto glucose, maltose, sucrose, and lactose ascitic fluid agar slants containing Andrade's indicator. The gonococcus ferments only glucose with the formation of acid.

It should be emphasized that "oxydase positive" colonies are not always gonococci. Approximately 1 per cent of the plates presented suggestive colonies which gave a strong positive oxydase reaction but were not gonococci. Three types of such confusing organisms were encountered: a gram-positive diplococcus, a gram-negative staphylococcus, and a gram-negative diplococcobacillus, which was very confusing in the primary plate but in pure culture produced a mucoid glistening growth quite unlike the gonococcus. This last organism is similar in form and pleomorphic tendencies to that described by Thompson,<sup>2</sup> but apparently differs in its inability to ferment the commonly employed differential sugar media. These three organisms are as yet unidentified but are being subjected to further study.

The spreads were stained by the Gram technique (Holman modification) and examined under the oil immersion objective for definite intracellular gram-negative diplococci.

\*Well isolated colonies are from 1 to 3 mm. in diameter with slightly undulated margins and are convex. By transmitted light they are transparent and almost invisible, while they appear grayish and somewhat opaque when viewed from the side.

†Sold by the Eastman Kodak Company as p-Amino dimethyl aniline monohydrochloride.

Bradford's (1934)	24	i	"Heart disease"	7 months	9 months	4 weeks	Spont. labor and delivery	Maternal blood	Living
Lieberman <sup>9</sup> (1934)	22	0	Rheumatism in childhood	Post partum	8 months	6 weeks	Spont. labor and delivery	Maternal blood	Living
MacRae <sup>10</sup> (1937)	27	0	Negative	6 months	Undelivered	Ante partum	Undelivered	Maternal blood	Undelivered. (Neg. cultures at autopsy)
MacRae <sup>10</sup> (1937)	27	iv	Chorea	"Near term,"	"Near term,"	Day of delivery	Cesarean section for abruptio placentae	Heart valves at autopsy	Stillborn (died from the abruptio placentae)
Felsen et al. <sup>11</sup> (1937)	25	?	Negative	7½ months	9 months	16 days	Spont. labor and delivery	Maternal blood, throat, urine, breast milk	Living. Negative cultures
Jensen <sup>12</sup> (1938)	27	ii	Rheumatic fever	7 months	8 months	2 months	Spont. labor and delivery	Heart valves at autopsy	Living
Page and Campbell	35	ii	Rheumatic heart disease	5 months	6 months	1 week	Spont. labor and delivery	Maternal blood	Died in 1 hour (Wt. 990 gm.)
Page and Campbell	30	ii	Rheumatic heart disease	2 months	3 months	Day of abortion	Spont. abortion	Maternal blood	Nonviable
Page and Campbell	20	0	Negative	7 months	8 months	1 month	Spont. labor and delivery	Maternal blood	Living. Negative cultures

*Monilia Cultures.*—In the ante-partum cultures monilia were grown from 146 patients (29.2 per cent). The fungus was present in 142 (29.7 per cent) of the controls and in 4 (20 per cent) of those with gonococci. It was associated with the trichomonads in 34 instances, including the 4 patients with gonorrhea, while in the remaining 112 individuals no other organism was grown. By contrast, monilia were cultivated only 11 times (2.2 per cent) in the postpartum series.

*Trichomonas Vaginalis Cultures.*—Trichomonads were cultured either before or after delivery from 113 (23.5 per cent) of the controls and from 7 (35 per cent) of the gonorrheal patients. No figures of relative incidence are available because post-partum cultures were not made in the early cases. Several patients had negative ante-partum but positive post-partum cultures, although in general the results agreed.

*Serologic Tests for Syphilis.*—There were 13 (2.7 per cent) positive reactors in the control group but none in those with proved gonorrhea.

*Clinical Data.*—Various clinical data for the 480 controls and for the 20 gonorrheal patients are presented in Table I.

TABLE I. CLINICAL DATA

	CONTROL GROUP (480)		GONORRHEAL GROUP (20)	
	NO.	PER CENT	NO.	PER CENT
Married	423	88.1	8	40.0
Unmarried, divorced, separated, and widowed	57	11.9	12	60.0
No previous pregnancies	225	46.9	8	40.0
One or more previous pregnancies	255	53.1	12	60.0
Average number of previous pregnancies in parous group (255 patients)	4.7		3.3	
History of previous abortions or miscarriages (255 patients)	80	31.4	3	15.0
Evidence of gonorrhea (history or examination)	7	1.5	10	50.0
Abnormal vaginal discharge	86	17.9	11	55.0

*Puerperal Course.*—Temperatures were recorded every four hours after delivery and the criteria for puerperal morbidity were those suggested by the American Committee on Maternal Welfare. By this standard only two (10 per cent) of the patients with cultural evidence of gonorrhea were "febrile," while in the control group there were 60 (12.5 per cent). In addition there were 6 patients (30 per cent) in the gonorrheal group and 80 (16.7 per cent) of the controls with temperature elevations to 100.4° F. or more which persisted for less than twenty-four hours.

To evaluate the risk involved in performing sterile speculum examinations during late pregnancy, individuals in the control group who were delivered on or before the fourth day after examination were compared with those who were delivered more than fifteen days after the speculum introduction. In the former (135 patients) the morbidity rate was 13.3 per cent as against 13.4 per cent in the latter (127 patients); and the one-day fever incidence was 16.3 and 15.5 per cent, respectively.

The two gonorrheal patients with febrile puerperiums developed their fevers early. One was delivered by low forceps and the other had a manual removal of the placenta. Both patients received sulfanilamide after appearance of the fever and apparently recovered promptly, although in one instance the gonococcus was demonstrated in the second culture. With the thought that the second-week syndrome might have developed after dismissal from the hospital (usually on the ninth or tenth day), follow-up letters were sent to the 20 gonorrheal patients. Replies were received from 15: one reported a "little" lower abdominal pain with urinary frequency, and another was operated upon for "appendicitis" (?) a few weeks after her return home.

*Identification of Monilia.*—The broth swab used to inoculate the first chocolate-agar plate was rubbed over the surface of a fresh moist Sabouraud's slant, which was then incubated at 37° C. for forty-eight hours, when smears were made from visible growths and stained by the Gram technique. The presence of large gram-positive, ovoid budding forms gave presumptive evidence of the presence of monilia. All positive cultures were re-examined after some weeks for mycelia and for ascospores (monilia do not form the latter structures). Although it is recognized that the term "monilia" is controversial, it is used here to designate the yeastlike organisms present in the vagina.

*Identification of Trichomonas Vaginalis.*—Material from each of the two areas was collected on a swab and inoculated immediately into a 5 per cent solution of human serum in Ringer's solution over a placenta-infusion-agar slant. After twenty-four hours' incubation at 37° C., the liquid was examined for typical motile organisms.

*Repeat Cultures and Spreads.*—Cultures and spreads were repeated on the eighth or ninth post-partum day immediately before the discharge examination. At first, trichomonas cultures were not made at this time but later the second examination duplicated that on admission.

*Serologic Tests.*—At the time of the first examination 8 c.c. of blood were drawn for serologic tests for both gonorrhea and syphilis. All of these tests were carried out in the Serologic Division of the State Hygienic Laboratory. The gonococcus complement fixation was performed according to the Kolmer technique using 10 units of Lederle's polyvalent gonococcus antigen. A modified New York complement fixation and the Kline presumptive test were utilized initially for the detection of syphilis and all positive reactors were further tested by the Kahn precipitin and the Kolmer complement fixation procedures.

## RESULTS

*Gonococcus Cultures.*—Among the entire series of 500 patients, the gonococcus was detected by culture in 20 (4.0 per cent). Nineteen yielded the gonococcus before delivery, while cultures from the remaining patient showed "oxydase positive" colonies but a marked overgrowth with *B. proteus* made it impossible to isolate the organism. Fourteen patients were shown to harbor the gonococcus after delivery: among the 6 with no cultural evidence of its presence at this time, 2 had received therapeutic doses of sulfanilamide; in one, technical difficulties probably prevented isolation of the organism; and in the remaining 3 there was no reasonable explanation for the change in findings. None of these 6 culturally negative individuals had positive spreads at either examination. Except in the one patient noted above, the post-partum culture did not show the gonococcus when that taken before delivery had failed to demonstrate its presence. In all the post-partum and in 13 ante-partum patients, there was no disagreement between the results of cultures taken from the cervix and the posterior vaginal fornix; but 6 ante-partum patients presented gonococci in only one area.

*Gram-Stained Spreads.*—Intracellular organisms fulfilling the staining and morphologic criteria for gonococci were demonstrated in material from both areas in 3 patients before delivery, but not in the remainder, while they were detected among the post-partum group in 12 of the 14 individuals with positive cultures. No definitely positive spreads were found among those patients who were negative on culture, although one case was "suspicious." In this instance, there was no serologic evidence of gonorrhea, but the patient presented an indurated Bartholin's gland.

*Gonococcus Complement Fixation.*—Among the group proved by culture to harbor the gonococcus, there was 1 "strongly positive," 2 "doubtful," and 17 (85 per cent) "negative" complement fixations. After delivery the "strongly positive" test became "negative." In the control group of 480 patients without cultural evidence of the gonococcus, there were 7 (1.5 per cent) "strongly positive" (1 was repeated and reported "doubtful"), 6 (1.3 per cent) "doubtful" (1 was repeated and reported "negative"), and 460 "negative" tests. Two sera were anticomplementary, and the test was omitted in 5 cases.



Certain clinical evidence cited by Thomas and Bayne-Jones,<sup>5</sup> supports the contention that the gonococcus "may not be pathogenic for all human beings." The lack of susceptibility of laboratory animals to gonococcal infection has so hindered the direct study of possible variations in virulence between different strains of gonococci that other indirect methods of approach have been utilized. Atkin,<sup>6</sup> and others, have attempted to correlate established clinical virulence, as evidenced by the severity of local and general reactions, with variations in the colony morphology on adequate media. The gonococci grown from acute cases of gonorrhea tend to form large, papilla-bearing colonies, while organisms from chronic cases may produce a preponderance of papilla-free colonies. This investigator has also demonstrated that old laboratory strains more commonly show the papilla-free growths. More recently, Casper<sup>7</sup> has stressed his belief that "the formation of papilla-free colonies is a sign of degeneration probably due to growth on artificial media," but that by adaptation to human tissues the organism may undergo similar degenerative alterations. This "degeneration" is attributed to loss of an essential carbohydrate which is specific for the particular strain. It is of some interest that in the majority of cultures obtained in the present study the usual colony was smooth and papilla-free or the papilla formation was only slight. In view, however, of the fact that a different medium was employed, definite conclusions will not be drawn pending further study now in progress.

#### CONCLUSIONS

Among 500 consecutive apparently normal obstetric patients, organisms satisfying the bacteriologic criteria for gonococci were cultivated from the vaginas or cervices of 20, an incidence of 4 per cent. Although a history suggestive of gonorrhea within eight years could be obtained from 10 of these 20 women, all were without manifestations of active infection at the time the cultures were made and consequently are viewed as "carriers." The puerperal course in these patients was not different from that of a control group.

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**Tynen, John:** Observations on Specimens of Human Semen, J. Contraception 4: 125, 1939.

Observations on more than five hundred specimens of human semen from 26 different men show that an average ejaculate has a volume of 3.9 c.c., contains 565 million sperms, and requires 3.0 c.c. of N/100 acid to neutralize 1.0 c.c. of the fluid.

HUGO EHRENFEST.

The eyes and vaginas of several of the babies of gonorrheal mothers were cultured immediately after birth. Gonococci were demonstrated five times in the eyes but no ophthalmia developed and cultures taken on the eighth or ninth day of life revealed no evidence of the organism. Routine prophylaxis consisted in preliminary flushing of the eyelids with 1:8,000 mercuraphen solution and the instillation of two drops of freshly prepared 1 per cent silver nitrate solution shortly after birth and again three hours later. The vaginas of four babies contained gonococci at birth, but, in spite of the absence of treatment, the organisms were uniformly absent in cultures taken on the eighth or ninth day.

#### DISCUSSION

It has long been suspected that certain individuals may be gonococcus carriers just as others are carriers for streptococci, pneumococci, meningococci, typhoid bacilli, and other pathogens. By the criteria usually employed, the women in whom the gonococcus was present but who had no clinical evidence of gonorrhea must be viewed as "carriers." In one-half of the group (10 patients) no history or stigmas of the infection could be elicited, while in the remainder the disease had evidently been contracted from six weeks to eight years previous to the first examination. In the older cases, the possibility of reinfection cannot be disregarded although the absence of any exacerbation of symptoms may be significant. Because of the lack of suitable experimental methods, it has been quite impossible to determine whether the gonococcus carrier state is due to increased resistance on the part of the host or to decreased virulence of the organism.

There is considerable evidence to indicate that under certain conditions the susceptibility of different tissues to gonococcal infection may vary from time to time. Newborn babies frequently develop gonorrheal ophthalmia following birth canal inoculations, but rarely, if ever, acquire vaginal infections even though gonococci may be grown from the vaginal introitus as demonstrated in some of the cases here recorded. This lack of susceptibility of the vaginal mucosa evidently represents a local tissue immunity, which is usually related to the character of the mucous membrane or to the acidity of the discharge. Bucura<sup>3</sup> in a series of 300 patients found that the titer of the complement fixation factor in blood from the cervix of infected women was higher than that in blood withdrawn from an arm vein, a finding which might be interpreted as indicating an increased local immune reaction in the pelvic structures. Pelouze<sup>4</sup> has also been prompted to suggest a changing local tissue immunity in explanation of certain clinical facts, such as the apparent increase in susceptibility of the genitourinary tract induced by the ingestion of alcohol, sexual excitement, and menstruation. In the series of "latent" infections here reported, the higher incidence of spreads containing gram-negative intracellular diplococci during the puerperium suggests a local increase in the number of gonococci, whereas the absence of general reactions and of symptoms pointing toward involvement of the tubes and uterus may indicate that the local protective mechanism was adequate to prevent the usual advance of the infection into the upper genital tract.

findings are consistent with a block of the right urinary tract, but whether it is due to a block in the lower ureter or to radiolucent calculi in the pelvis of the kidney cannot be determined. Recommend unilateral retrograde pyelography (right)."



Fig. 1.

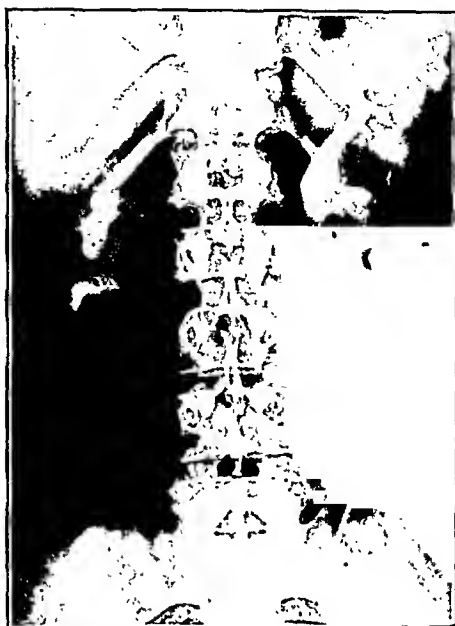


Fig. 2.



Fig. 3.

On March 30, 1939, two days later, cystoscopy revealed edema about the right ureteral orifice from which no urine dropped. An ureteral catheter was inserted through the right ureteral orifice for a distance of 15 cm. at which point an impassable obstruction was met. Intravenous injection of indigocarmine was followed by normal excretion on the left side and no excretion on the right side. The diagnosis at this time was occlusion of the right ureter at the approximate level of the infundibulopelvic ligament.

## POSTOPERATIVE URETERAL OBSTRUCTION DUE TO PTOSIS OF THE KIDNEY\*

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IN A RECENT review of the literature on postoperative ureteral injuries, no reference was found demonstrating complete blockade of the ureter caused by kinking associated with ptosis of the kidney.<sup>1</sup> We are reporting the following case because it demonstrates the importance of considering acute ureteral kink in the differential diagnosis of the causes of postoperative ureteral obstruction.

Mrs. A. P., aged 47 years, was admitted to the hospital March 16, 1939, with a diagnosis of a midline lower abdominal tumor, the approximate size of a twenty to twenty-two weeks' gestation. Her last menstrual period was on Jan. 10, 1939, prior to which time she had menstruated monthly. The past history was negative medically and surgically. There was one full-term pregnancy at the age of 30, which terminated uneventfully. The puerperium was uneventful. General physical examination disclosed no pertinent findings. Rectovaginal abdominal examination revealed a large cystic mass rising out of the pelvis and reaching to the umbilicus. The mass was nontender and freely movable. The uterus was small, firm, and fixed to the right just behind the symphysis pubis by pressure from the tumor. To the left a firm cystic mass approximately 8 by 8 cm. in diameter was felt protruding into the left vaginal fornix. The erythrocyte count was 4,400,000; hemoglobin, 80 per cent (Tallqvist); leucocytes, 8,800; and sedimentation time, seventy minutes. The blood pressure was 66 systolic and 94 diastolic. The urine showed a trace of albumin, but was otherwise negative.

On March 17, 1939, laparotomy was performed. On opening the abdomen a large cystic mass presented itself, filling the entire lower abdominal cavity. The cyst had its origin on the left side and the left Fallopian tube was thinly spread on its upper surface. The left ovary was separately identified and seemed to be replaced by a hard dermoid cyst approximately 5 by 5 cm. in diameter. The large tumor was therefore a huge left intraligamentary cyst. The right ovary was normal. The right broad ligament contained an intraligamentary cyst approximately 4 by 4 cm. in diameter. Because of the bilateral adnexal pathology, and because of the patient's age, a supravaginal hysterectomy and bilateral salpingo-oophorectomy were done, including the parovarian cysts. This was preceded by aspiration of two quarts of clear fluid from the large cyst in order to reduce its size. Patient left the operating room in good condition.

The postoperative course was uneventful until the fifth day when the patient complained of a persistent dull pain on the right side, radiating from the costo-vertebral area anteriorly and downward to the groin. Palpation revealed an enlarged tense kidney, the lower pole of which reached to the level of the iliac crest. This renal swelling was markedly tender, and it was suspected that the enlargement of the kidney may have been due to a right ureteral injury. The urine at this time was negative.

On March 28, 1939, eleven days postoperatively, excretion urography was done (Fig. 1). The roentgenologic report was as follows: "Left kidney normal. The right kidney fails to show concentration, except to a very minor degree in a dilated lower calyx at fifteen minutes and no further function is shown. The right kidney is considerably enlarged in comparison to the opposite side. The

\*Presented at a meeting of the Chicago Gynecological Society, May 19, 1939.

literature showed that vasa previa is very often associated with intra-partum death of the fetus. In most of the cases reported, a diagnosis was not made until the fetus was in very poor condition, hence the treatment was usually unsatisfactory.

The etiology is not fully understood, but the explanation of Franque is considered the most acceptable theory: that the abdominal pedicle ordinarily extends from the fetus to the most vascular portion of the chorion. This is usually in contact with the decidua basalis and therefore the cord becomes inserted into the placenta. Sometimes, early in pregnancy, the most vascular portion of the chorion is the decidua capsularis; hence the abdominal pedicle will become attached to this unusual location. With the continuation of pregnancy, there will be a shift of vascularization to the decidua basalis, but the abdominal pedicle, retaining its original position thus produces a velamentous insertion of the cord. The following case is reported because of its many unusual features:

The patient, aged 20 years, a primipara, was first seen on June 14, 1937, at which time examination revealed a pregnancy of about thirty-two weeks' duration. The last menstrual period occurred on Dec. 27, 1936, and the probable conception date of Jan. 2, 1937, was given. Life was felt on May 9, 1937, and from the menstrual data, term was estimated at Oct. 4, 1937. The size of the abdomen was out of proportion to the estimated duration of the pregnancy, and twins were diagnosed; an x-ray examination corroborated the clinical findings. The prenatal course was uneventful until Aug. 24, 1937, when urinalysis revealed three-plus albumin with many pus cells in the sediment; the blood pressure was 122/76. The blood pressure rose steadily to 148/90 during the following two weeks, and the albuminuria persisted with the additional finding of finely granular casts. The patient was treated conservatively, viz: bed rest, salt-free diet, and magnesium sulphate by mouth. Because she failed to respond to this medical management of her toxemia, induction of labor was instituted by the administration of castor oil, soap-suds enema, and 5 gr. of quinine sulphate. This procedure was not successful until repeated twice in a period of seven days. The membranes ruptured shortly after uterine contractions began, and coincident with the spontaneous rupture of the bag of waters, there was a sudden gush of about one pint of dark red blood followed by a steady trickle of blood resembling the "show." Abdominal palpation at this time revealed that the twins were both in cephalic presentation, and the head of the first fetus was deeply engaged. The fetal heart tones over each fetus were believed to be satisfactory. Rectal palpation twenty-five minutes after the onset of labor found one head on the pelvic floor and the cervix effaced and 5 cm. dilated. The patient was watched closely; soon she began to bear down spontaneously. Since the vaginal bleeding had diminished, the maternal pulse was 80, and the fetal heart tones of both babies appeared to be of good quality, we decided to permit the patient to deliver spontaneously. However, when no progress was noted forty-five minutes after the onset of the second stage, a mediolateral episiotomy was performed and low forceps were applied to the head in a right occipitoanterior position, and delivery of the head was easily effected. A pulseless thin cord was found once around the neck; the cord was cut between two clamps and the first twin, a boy weighing 5 pounds, 5 ounces, was extracted. The baby showed no signs of life and failed to respond to tracheal catheterization, application of external warmth, and intracardiac administration of adrenalin solution. The fetal heart tones of the second twin were good, and since there was no further bleeding, the delivery was delayed in order that the overdistended uterus be given time to retract. The second bag of waters was ruptured artificially fifteen minutes later and the baby delivered after manual rotation of the head from a left occipitoposterior position and the application of low forceps. The second male infant cried spontaneously and seemed vigorous; it weighed 5 pounds, 12 ounces. The placenta was delivered by early expression and was followed by a post-partum hemorrhage estimated at about 750 c.c. of blood. The uterus was promptly packed

During the subsequent week, the temperature varied from 98.8° to 100.4° F., and the urine was negative except for an occasional leucocyte. The patient improved under conservative management, gained weight, and the kidney mass was apparently slowly receding. The patient was discharged on the eighteenth postoperative day. At home there was continued improvement. The pain subsided, the patient continued to gain weight, and there was a progressive diminution in the size of the "renal mass."

Excretion urography on May 1, 1939 (thirty-four days after cystoscopy), was reported as follows: "The lower pole of the left kidney is at the level of the transverse process of the third lumbar vertebra, and the lower pole of the right kidney is at the level of the upper margin of the fourth lumbar vertebra. The renal pelvis on the right side appears to be larger than on the opposite side and the calyces appear to be slightly blunted (Fig. 2). A film taken with the patient upright reveals the lower pole of the left kidney to have descended to a point opposite the transverse process of the fifth lumbar vertebra, and the lower pole of the right kidney is seen to be at the level of the second sacral vertebra. The distortion of the ureters may be seen on both sides, and particularly on the right side is there noted a marked angulation in the renal pelvis and ureter." (Fig. 3.)

In our opinion the above recorded case and illustrations demonstrate that a ptosed kidney may be held upright by a large pelvic tumor. On removal of the tumor the kidney may drop and the associated acute angulation of the ureter produce findings similar to those which occur with ligation of the ureter. The only other possibility to be considered in this case is the re-establishment of kidney function following the resorption of an encircling catgut ligature. This, however, seems unlikely in view of the work of Caulk<sup>2</sup> who found that catgut will never absorb before the death of the kidney.

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58 EAST WASHINGTON STREET

## VELAMENTOUS INSERTION OF CORD WITH SPONTANEOUS RUPTURE OF VASA PREVIA IN TWIN PREGNANCY\*

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VELAMENTOUS insertion of the umbilical cord is an unusual finding in the routine examination of the placenta. It has no clinical significance unless the vessels of the cord are so situated that they are either torn or compressed during labor. Such accidents are more likely to occur when the vessels are located in the lower uterine segment, the so-called vasa previa, but Kosmak reported a case in which rupture of a velamentous cord in the vicinity of the fundus of the uterus occurred.

The incidence of velamentous insertion of the cord is variously given as occurring in about 1 per cent of cases. Williams found it in 1.25 per cent of his cases and quoted Lefèvre who cited an incidence of 0.84 per cent in 15,891 placentas examined. This anomaly is nine times more frequent in twins, and DeLee states that it is almost routine in triplets. A study of the available

\*Presented at a meeting of the Chicago Gynecological Society, May 19, 1939.

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185 NORTH WABASH AVENUE  
310 SOUTH MICHIGAN AVENUE

## TUBERCULOSIS OF THE PLACENTA

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**T**UBERCULOSIS of the placenta is an infrequent occurrence. Williams<sup>1</sup> had never seen a case in the several thousand placentas he examined at Johns Hopkins Hospital. In 1922, Whitman and Greene<sup>2</sup> collected 44 cases from the literature in which both tubercles and tubercle bacilli were demonstrable in the placenta. There have been no other cases reported in the American literature since their paper appeared. In 150 consecutive placentas of tuberculous women examined at Sea View Hospital, there was only one case of placental tuberculosis.

The following is the report of a case of tuberculosis of placenta in which both a tuberculous focus and acid-fast bacilli within the focus were demonstrated and in which both mother and infant have been followed for two and one-half years.

A. G., a 29-year-old, colored housewife, was admitted to Sea View Hospital in June, 1936. She had had three normal, full-term pregnancies in 1932, 1934, and 1935. Her first infant died at the age of two years of meningitis. The other two children are living and well. The onset of her tuberculosis was in November, 1935, with cough and expectoration. Pulmonary tuberculosis and pregnancy were diagnosed by the Health Department Clinic, and she was sent to Bellevue Hospital. She was transferred to Riverside Sanatorium in January, 1936, where she received a left initial pneumothorax in May, 1936. Refills were given twice weekly, and she was sent to Sea View Hospital in June, 1936. Here her pulmonary lesion was diagnosed as caseous-pneumonic tuberculosis of the left lung and exudative disease in the right upper lung. Her sputum was Gaffky X before delivery. She delivered spontaneously after an eight hour labor in September, 1936. The infant showed no abnormalities and was immediately removed to a nontuberculous ward. Following delivery the mother received refills. She is still at Sea View Hospital and has been scheduled for thoracoplasty. Her pelvic examination is entirely negative.

The infant was watched carefully. The neonatal period was normal except for cyanosis during the first month. He was always plump and robust but had miliaria and mild rickets, from which he recovered. Repeated x-rays of the lungs, gastric analyses for tubercle bacilli and the Mantoux test up to 1 mg., were all negative. The infant was transferred to The New York Foundling Home in September, 1937, and is there at the present time. He is in good condition and shows no evidence of tuberculosis.

Gross examination of the placenta revealed a yellow area about 7 mm. in diameter. The placenta was otherwise not remarkable. Microscopic sections through this area (Fig. 1) showed an irregular oval area composed of pink granular material with fine nuclear fragments. This area is surrounded by a narrow reticulum of capillaries, fibrils and histiocytes. There are irregular projections into this granular area on one of which are intact polymorphonuclear leucocytes and round cells. There are a number of thin-walled blood vessels in and adjacent to the granular area. Acid-fast bacilli were described in the Ziehl-Neelsen stain.

and the episiotomy repaired; although the mother's condition was only fair, she responded well to the administration of 1,000 c.c. of 10 per cent glucose solution intravenously.

Inspection of the placenta proved very interesting. It was a single large placenta, weighing 950 gm.; the membranes were composed of two amnions and but a single chorion, typical of monochorial twins. The cord of the first twin was inserted into the membranes in the lower uterine segment as a velamentous insertion. The original rupture of the membranes extended into and perforated a large blood vessel branch of this velamentous inserted cord (see Fig. 1).

This case is of interest chiefly because of the difficulties in diagnosis. Vasa previa is seldom diagnosed before delivery because of its rarity, and the possibility of its occurrence is rarely considered. Very few cases reported in the literature were diagnosed before delivery and the subsequent examination of the placenta. Because of intra-partum bleeding the condition is usually confused with premature separation or placenta previa. The underlying toxemia led us to believe that we were dealing with a mild case of premature separation of the placenta. Vasa previa should be considered whenever bleeding occurs at the time of rupture of the membranes, associated with a well-engaged presenting part, especially when a multiple pregnancy exists. Diagnosis may even be made before rupture of the membranes, if on vaginal examination pulsating vessels are

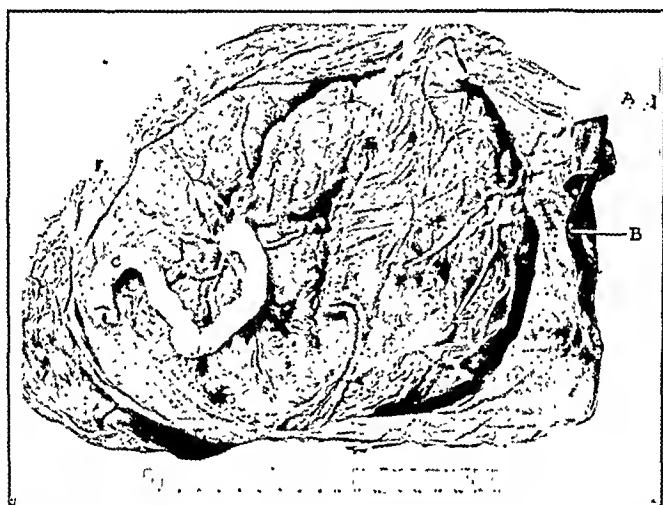


Fig. 1.—Placenta, velamentous insertion of cord of first twin (A), showing vasa previa ruptured (B), cord of second twin centrally inserted (C).

palpated in the membranes. Frommolt and Terasvuori described cases of bleeding prior to rupture of the membranes with intra-partum death of the fetus. In our case, the intra-partum bleeding had occurred from a ruptured branch of an umbilical artery on the maternal surface of the membranes.

The treatment is usually very unsatisfactory since the diagnosis of vasa previa is almost never made before actual rupture of an umbilical vessel occurs; after rupture, the fetus rapidly bleeds to death. When such bleeding occurs, the fetus shows signs of distress and heart tones rapidly fail. In our case, the detection of good heart tones in two locations led us into a false sense of security. Undoubtedly, we were eliciting the heart tones of the second and normal baby in two distinct regions of the abdomen.

In the case of monochorial twins, both may die from exsanguination following rupture of but a single vessel. The second twin showed no sign of asphyxiation or exsanguination; therefore, one may assume either that the loss of blood was insufficient to affect the more vigorous twin or that little or no collateral circulation existed between the two halves of the placenta. The occurrence of post-partum hemorrhage in this case in all likelihood was due to the rapid labor and the overdistention of the uterus in a twin pregnancy.



fields, but showed marked cardiac enlargement with an unusually straight left border "suggestive of a mitral lesion." Daily urine examination disclosed increasing numbers of red blood cells and casts.

The patient continued to run a low grade fever and developed symptoms of congestive heart failure in spite of sedation and adequate dosage of digitalis. Therapeutic abortion was advised, but on the morning of Feb. 5, 1937 (eight days after admission), a complete spontaneous abortion occurred with minimal blood loss. Respiration became laborious, auricular fibrillation followed, and she died two hours later.

The clinical diagnosis was (1) rheumatic heart disease, mitral stenosis and regurgitation, *Streptococcus viridans* endocarditis, with congestive heart failure, and (2) three months' pregnancy with spontaneous abortion.

At autopsy the clinical impressions were confirmed. The heart weighed 450 gm. The pericardium contained 300 c.c. of clear fluid. The left ventricle was enlarged, the myocardium thickened but free from scars. The endocardium showed scarring and large, soft, granular vegetations about the mitral valve. There was marked narrowing of the mitral opening. In addition to the cardiac findings there were recent small infarcts of the right kidney cortex, a right pleural effusion, chronic passive congestion of the lungs, liver and spleen, and septic emboli to the peritoneum. The right ovary contained the corpus luteum of pregnancy. The uterus was enlarged, softened, and contained decidual fragments.

(Permission to include this case was kindly granted by Dr. Benjamin Black and Dr. J. L. Eaton.)

CASE 3.—A 20-year-old white primigravida applied for prenatal care in March, 1937, during the second month of her pregnancy. During childhood she had had bronchopneumonia three times and frequent attacks of tonsillitis, but no rheumatic or scarlet fever or other serious illnesses. The family history was of no significance.

On the initial examination no unusual findings were noted. She was a healthy girl, 5 feet 5 inches tall, weighed 117 pounds, and had a normal pulse rate and temperature. The blood pressure was 115 systolic and 60 diastolic. The heart was not enlarged to percussion, the rhythm was regular, sounds were of good quality and no murmurs were detected. The lung fields were clear. Pelvic measurements were within normal limits, and the pelvic examination revealed the usual signs of an eight weeks' pregnancy. The hemoglobin was 75 per cent (Sahli), and the blood Wassermann negative. The urine was negative for albumin and sugar, and showed no formed elements on microscopic examination.

With the exception of a moderate amount of nausea and vomiting, the prenatal course was entirely uneventful until Aug. 30, 1937 (two months from term) when she complained of a persistent dry cough. Examination disclosed a temperature of 99.4° F., pulse rate 130, respiratory rate 28, and blood pressure 110 systolic and 80 diastolic. Crackling râles could be heard over both lung fields posteriorly. A loud systolic murmur and a crescendo presystolic murmur could be heard over the entire precordium. She was put to bed and given digitalis and a cough mixture.

The cough continued unabated and she developed dyspnea, orthopnea, frequent epistaxis, and occasional blood-tinged sputum. There were night-sweats, and in the evenings her temperature was found to be 100° F. or slightly higher. A blood count on September 7 (ten days after the onset of her illness) showed the hemoglobin to be 50 per cent Sahli (a drop of 25 per cent since her first examination), 2,800,000 red blood cells, and 12,500 white blood cells with 18 per cent unsegmented forms.

A diagnosis of bacterial endocarditis was made and two blood cultures showed a delayed growth of *Streptococcus viridans*, the colonies appearing in five and seven days, respectively.

The symptoms of cough, palpitation, nausea, indigestion, orthopnea and fever continued in spite of symptomatic treatment, and she entered a private hospital on September 24. The consultants were unanimously opposed to interruption of the pregnancy at this stage, feeling that such a procedure would hardly alter the unfavorable maternal prognosis, while the chances for survival of the baby were good.

Before making a diagnosis of placental tuberculosis both tubercle bacilli and tuberculous changes should be demonstrated in the placenta. Using these criteria, only 44 cases have been reported in the literature up to 1922. No cases have been reported in the American literature since that date. Although a rare finding, the importance of placental tuberculosis cannot be over-emphasized. In the clinically unsuspected case of tuberculosis, the finding of tuberculosis of the placenta is evidence of a hematogenous tuberculosis in the mother. Every effort should be made to find the focus of infection which may be in the lungs, in the bronchus, in the



Fig. 1.—Photomicrograph of the placenta which shows an area of necrosis (a) in which acid-fast bacilli were found. Surrounding the area of caseation is a narrow zone of tuberculous granulation tissue (b). The normal placental tissue (c) is present beyond the zone of tuberculous granulation tissue.

skeletal system, in the genitourinary tract or in the gastrointestinal tract. One cannot make a definite statement as to the frequency of placental tuberculosis from the one case described above. Since only several sections of the placenta are examined microscopically, it is a simple matter to miss a small tuberculous focus. Schmorl<sup>3</sup> stated that he had to make over two thousand sections of a placenta before demonstrating tuberculosis in one case. Perhaps some method of culturing the entire placenta would yield a higher percentage of positive results.

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## TUBAL PREGNANCY WITH TUBERCULOUS SALPINGITIS\*

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J. R., A MEXICAN woman (Case C55288), aged 29 years, married eight years, nulliparous, was admitted to the hospital as an emergency on Feb. 16, 1939, because of vaginal bleeding and severe lower abdominal pain. Menses started at 13 years of age, were regular, of the twenty-eight-day type, from 4 to 6 days' duration, scant and without pain, last period Nov. 22, 1938. Although the patient had never used contraceptives, no pregnancies had occurred in the eight years of marriage.

For the past six weeks she had suffered attacks of severe abdominal pain accompanied by bleeding. In the past week, the pain had been more severe and had occurred daily; the flow had been more or less continuous but scanty. The pain was intensified by emptying the bladder and rectum. Except for frequent colds, the past history was negligible. Although she had been under observation at the Municipal Tuberculosis Sanatorium as a contact (one sister had tuberculosis), no diagnosis had been established.

Examination revealed a short, stout woman who was quite pale and in severe pain. During the examination, repeated coughing appeared to aggravate her abdominal pain and also led her to complain of pain in the right shoulder. Examination of the chest revealed no findings. The breasts were hypertrophied and the areolae pigmented. The abdomen was soft in the upper portion but rigid below. There was marked tenderness throughout the hypogastrium. Vagino-abdominal examination revealed a nulliparous cervix which was felt high up near the symphysis, behind which was a definitely bulging cul-de-sac. The mass appeared to fill the true and false pelvis, obliterating the touch for uterus and adnexa. The external os was closed and a blood-stained discharge followed the vaginal examination. Upon percussion, the lower abdomen was *flat*. Temperature was 100.8° to 101° F. (R.); pulse, 92-100; and respirations, 24; the white blood count was 12,800; hemoglobin, 45 per cent; red blood count, 1,140,000; the Kahn test was negative; blood pressure was 106/64.

The diagnosis of ectopic pregnancy which was made was quite obvious, with a large hematocele and probable presence of clots, indicating slow intraperitoneal bleeding for some time previously. The diagnosis was further substantiated by the presence of marked anemia and the absence of shock.

After administration of 1,000 c.c. of 5 per cent glucose in saline by venoclysis, laparotomy was performed under cyclopropane-oxygen anesthesia. Upon opening the peritoneal cavity, a large amount of blood and old dark clots was found, and upon removing the latter, a well-formed fetus, 5 cm. in length, and a placenta, 8 cm. in diameter, were found in the right iliac fossa. The placenta was loosely attached to the omentum but entirely free of the right tube, near which it was found. The right tube and ovary were firmly matted together by dense fibrous adhesions and were adherent to the posterior surface of the broad ligament. The fimbriated end of the tube and ampulla were greatly dilated and actively bleeding. Right salpingo-oophorectomy was done. The left adnexa were likewise bound down, but the ovary was less extensively involved. The tube was thick and spindle-shaped in the ampullar region, with a constricted but patent fimbriated end. The tube was removed, but the uterus, which was normal in size, and the ovary were left in situ. A postoperative diagnosis of tubal abortion with extensive intraperitoneal hemorrhage was made. After closing the abdomen, 500 c.c. of whole blood was transfused by the direct method. During the operation, the pulse slowed from 100 to 80, and respirations dropped from 24 to 18 per minute.

\*Presented at a meeting of the Chicago Gynecological Society, May 19, 1939.

The pathologic report revealed a *tubal pregnancy with tuberculous salpingitis*. *Pathologic Diagnosis:* Fetus, Placenta, Tube and Ovary: The specimen consisted of multiple fragments of tissue of a variable consistency, comprising a fetus, which, reconstructed, measured 5 cm., a mass of spongy pinkish purple tissue, and a saccular structure, measuring 8 cm. in circumference, the concave aspect of which was granular, trabeculated, and hemorrhagic, and measured 0.8 cm. in thickness. Another specimen consisted of thickened, somewhat dilated segments of Fallopian tube, measuring 8 cm. in length. To this was adherent hemorrhagically discolored fat tissue.

The distal end of the tube was sealed. In the mesosalpinx was an oval structure (ovary) which measured 3 by 1.5 cm. in the greatest dimensions. Its sectioned surface was grayish white, glistening, with minute yellow and larger grayish-white dots. A third specimen consisted of a cord of fat tissue to which was applied dark, brownish red material which resembled clotted blood. Also present was a partially open and sectioned, thin, tubular structure, measuring 6 cm. in length. Adherent to its external surface was a crust of brownish red material.



Fig. 1.

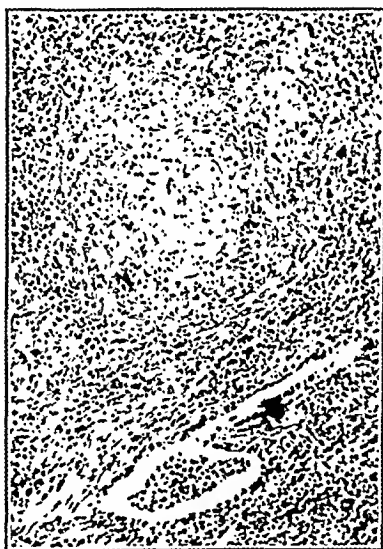


Fig. 2.

Fig. 1.—Tuberculous salpingitis, seat of tubal abortion (magnification,  $\times 100$ ).

Fig. 2.—Tuberculous salpingitis (magnification,  $\times 110$ ).

*Histologic Description of the Tube.*—The Fallopian tube was diffusely infiltrated with lymphocytes, polymorphonuclear leucocytes and occasional endothelial cells. Scattered throughout were also discrete concentric masses of cells which were fairly well demarcated from the adjacent tissues. These cells were for the most part somewhat elongated, had pale vesicular nuclei and resembled epithelioid cells. Frequently in the center of such a nest of cells a multinucleated giant cell with nuclei arranged about the periphery of the cell was seen. This mass of cells was surrounded by a zone of lymphocytes intermingled with which were occasional large mononuclear leucocytes. Areas of necrosis were found throughout the sections. In some of the sections, adherent to necrotic structureless masses of tissue in which were many extravasated red blood cells, typical chorionic villi were recognizable.

*Report of Endometrial Biopsy Specimen.*—Throughout the endometrium were seen many accumulations of cells similar to those described in the Fallopian tube. These were arranged to form typical tubercles composed of epithelioid cells, multinucleated giant cells and lymphocytes. In some portions adjacent tubercles had fused forming larger conglomerate tubercles. Areas of necrosis were seen throughout.

The first 6 postoperative days were febrile and characterized by coughing, but convalescence was otherwise satisfactory. No pulmonary lesions were found upon repeated chest examinations by medical and tuberculosis consultants; likewise, x-rays of the chest, sputum examinations, and blood cultures were all negative. On the sixteenth day, hemoglobin was 60 per cent; red blood count, 3,200,000; white blood count, 8,200; temperature, pulse, and respiration, normal. The patient was discharged from the hospital on the twentieth postoperative day.

Follow-up in the clinic one month after operation revealed a good primary union of the abdominal incision; convalescence was satisfactory. Endometrial biopsy (made by Dr. Tulsky in the course of research) revealed tuberculous endometritis. It is planned to continue the follow-up of this patient with oxyperitoneum.



Fig. 3.

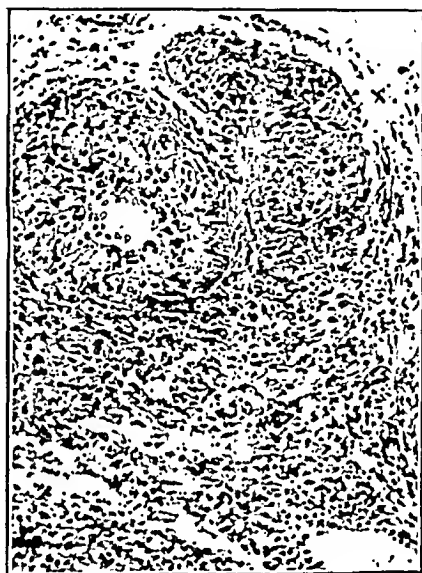


Fig. 4.

Fig. 3.—Placental tissue lying free in the peritoneal cavity (magnification,  $\times 56$ ).

Fig. 4.—Endometrial biopsy, tuberculous endometritis (magnification,  $\times 140$ ).

In this case, tuberculosis of the genitalia apparently existed for some time but produced no symptoms of the disease. The menses were regular and there was no pain. The only possible hint of genital disturbance was the long period of sterility. She was a tuberculous contact, one sister being under treatment; however, no pulmonary involvement was found either before or after operation in this patient.

Tubal pregnancy is a very rare complication of tuberculous salpingitis as was recently brought out by Stevenson and Wharton.<sup>1</sup> According to these investigators, only 8 cases previous to theirs have been reported in the medical literature. Furthermore, in the forty-seven years of the existence of the Johns Hopkins' Gynecological Pathology Laboratory, there were 402 cases of tuberculous salpingitis and 516 of tubal pregnancy recorded without a single instance in which the two conditions were combined. Stevenson and Wharton report one such case and discuss the condition in full. Our case, which closely resembles theirs in many respects, is the tenth to be reported in the medical literature of tubal pregnancy associated with tuberculous salpingitis. In addition, a tuberculous endometritis was demonstrated by endometrial biopsy.

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## PRIMARY CHORIONEPITHELIOMA OF THE FALLOPIAN TUBE

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CHORIONEPITHELIOMA of the Fallopian tube is a condition which occurs very infrequently. Recently the thirty-fifth case was reported by R. L. Pearse and C. K. Fraser.\* Since their article furnishes a complete bibliography and reviews the literature to the present time, only a simple case report will be presented.

On July 19, 1938, Mrs. G. C., aged 45 years, entered St. Anne's Hospital complaining of pelvic pain associated with a sensation of pressure. The pain was constant, dull, aching in type, located in the lumbrosacral region, and had been present for five years. Her menstrual periods had been abnormal also for the past five years characterized by a fourteen-day cycle with profuse bleeding. In the six months prior to entrance she had lost nine pounds in weight.

Past history disclosed that she was married when nineteen years of age. One year later her first child was born with no abnormalities in the labor, delivery, or puerperium. No past history of ectopic gestation, suggestive or otherwise, was obtained. She had no abortions either spontaneous or induced. During 1923 a whitish vaginal discharge had been present for a few months and then subsided spontaneously.

Complaints referable to the pulmonary system were not elicited except for a few previous attacks of laryngitis during the winter months.

Examination revealed a fairly well-nourished and well-developed white female. Temperature, 98.6° F.; pulse, 84; respiration, 16; blood pressure, 136/78. All findings including examination of the chest were essentially negative except for the pelvic examination.

Pelvic examination revealed a uterus the size of a three months' pregnancy which was distinctly nodular and firm. In the right adnexa was an elongated mass definitely distinct from the body of the uterus. The preoperative impression was myofibromas of the uterus with an associated right adnexal mass, possibly an ectopic pregnancy.

Laboratory findings were as follows: hemoglobin, 80 per cent; erythrocyte count, 4,070,000; leucocytes, 6,000; differential, normal. The urine was negative and the Aschheim-Zondek test was begun on July 19, 1938, because of the possibility of an ectopic pregnancy. Three days later it was returned positive, but by this time the surgery had been performed.

Operation was performed on July 20, 1938. A midline suprapubic incision was made. The mass in the right tube was seen to be about the size of an orange and occupied the middle and distal portion of the tube. It was adherent to the cecum but these adhesions were easily separated. The tumor was removed intact. Both ovaries were moderately atrophic. The left tube was apparently normal. There was no glandular involvement in the pelvic region.

The uterus was well above the symphysis and contained several subserous and intramural fibroids. Supracervical hysterectomy with bilateral salpingo-oophorectomy was performed and the abdomen closed without drainage.

The pathologic report of the specimen described above showed uterine fibroids, the largest was 3.5 cm. in diameter. The tubal tumor grossly was a separate

\*AM. J. OBST. & GYNEC. 35: 1046, 1938.

roughly oval mass (9 by 7 by 4.5 cm.). The surface was smooth with small protruding nodules. The cut surface was rough, yellowish pink in color and spongy in consistency. There were conspicuous trabeculae separating the spongy tissue into rounded areas. The microscopic sections of the tumor of the tube were those of a highly malignant tumor of the chorionepithelioma type.

The postoperative course was uneventful until the seventh day, when there was a trace of blood in the sputum. An x-ray of the chest was as follows: "Examination of the chest shows a circumscribed opacity in the region of the left hilus. There is also a cloudiness in the lower left lung field. In view of the patient's history these changes are very suggestive of metastases. However it would be advisable to re-examine the patient after a short interval."

X-ray therapy was begun at this time. Daily treatments over the anterior chest from July 8, 1938, to Aug. 13, 1938, were given, consisting of 171 roentgen units, 200 kilovolts, 25 milliamperes,  $\frac{1}{2}$  copper filter, 50 cm. distance, and a 20 cm. field for three minutes.

On the eleventh postoperative day the sutures were removed and the patient was allowed to use the back rest. On the twelfth day very labored respirations with air hunger occurred accompanied by considerable bloody expectoration. This condition recurred several times at subsequent intervals. On the nineteenth day the second chest x-ray showed the following changes: "Examination of the chest shows the circumscribed shadow about the left hilus to be slightly more pronounced than at the last examination. In addition, there are definite soft circumscribed shadows in the lower left lung field. The right hilus shadow is also prominent but no definite changes can be seen in the remaining portions of the previous impression of metastases."

On the twenty-fourth postoperative day (Aug. 13, 1938), the patient suddenly became very dyspneic and died in spite of the usual emergency methods of treatment. Autopsy was not permitted.

#### COMMENT

The case reported illustrates the difficulty in diagnosis and the highly malignant nature of chorionepithelioma. This patient was particularly interesting because of the absence of any symptoms indicating a previous ectopic pregnancy and the short interval between the operation and the metastases to the lungs.

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Page, Seager and Ward: The Use of Placental Blood for Transfusion, *Lancet* 1: 200, 1939.

The authors' experience with placental blood for use in transfusions has been satisfactory. Careful collection is necessary to insure sterility; 1 gm. of sodium citrate in 80 c.c. of twice distilled water is used as an anticoagulant. The third stage of labor is not prolonged by draining the placenta. Blood counts taken on the first, second, seventh, and fourteenth days of life in 12 infants showed no appreciable difference from those in 12 control infants. Mild icterus developed in 2 of the controls and in 1 of the placental group. The average yield of blood was 80 c.c. Placental blood of the same groups may be mixed to provide for a large transfusion. Reactions are not increased by using placental blood. It is stored at 33 to 38° F. and should not be heated before use. The flask is allowed to stand at room temperature one-half hour before use and if the drip method is used, this is unnecessary.

CARL P. HUBER.

## CARCINOMA OF FUNDUS IN COMPLETE PROCIDENTIA

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CARCINOMA of fundus in complete procidentia is extremely rare. There are only 5 proved cases reported in the literature, and 3 doubtful cases which might have been carcinomatous at the time an interposition operation was done two or three years previous to the discovery of the malignancy.

Scheffey<sup>1</sup> from the Jefferson Medical College Hospital in 1934 reported 2 cases of adenocarcinoma of the uterus associated with complete procidentia. Two cases are mentioned by Guthrie and Bache<sup>2</sup> and one by Bissell.<sup>3</sup> Bissell also mentions 2 cases of adenocarcinoma of the uterus three years after interposition for complete prolapse, and a similar case is described by McGlinn,<sup>4</sup> whose paper Bissell discussed at the fifty-second annual meeting of the American Gynecological Society in 1927.

### CASE REPORT

J. G., a 59-year-old white female, was admitted to Cumberland Hospital, on April 22, 1936, complaining of a "dropped womb" of fifteen years' duration.

Fifteen years before she had been told that she had a prolapsed uterus, but she refused operative interference. For the past ten years she had constantly worn a vulvar pad, as the uterus "dropped out" and interfered with walking. For the past two years she had had a marked vaginal discharge, which during the last three months had become sanguineous.

She began to menstruate at the age of 11, each period lasting three days. She had always been "regular." The patient had had three children, two of whom are living, one having died in infancy. Her menopause began nine years ago.

Examination revealed a well-developed, well-nourished female, weighing 174 pounds. Her chest showed evidence of chronic bronchitis. She was a hypertensive cardiac, Class 2B, with a systolic pressure of 240 and diastolic of 130. The abdomen was tympanitic and distended. She had a large cystocele and rectocele. The entire cervix and lower segment of the uterus protruded from the vagina; the cervix was lacerated and dry, having the consistency of parchment. There was no evidence of any bleeding.

The urine showed a trace of albumin. The blood count was within normal limits. The blood Wassermann was negative. The blood chemistry showed: sugar 110 mg., urea 16.7, uric acid 4.3, creatinine 1.6.

Again she was very reluctant to undergo any operation, and was therefore given supportive treatment for her hypertension and cardiac condition, and kept under observation.

Two months later her abdomen became progressively distended and showed evidence of ascites. On July 18, 4,000 c.c. of yellow fluid was removed by abdominal paracentesis. After the removal of the fluid a mass was felt in the right lower quadrant. The uterus was fixed in the pelvis and could not be displaced. She developed a low grade temperature. On August 3, 3,600 c.c. of fluid was removed. She began to lose ground very rapidly and died on August 12.

An autopsy was performed by Dr. Polayes, the pathologist. The final anatomic diagnoses were as follows: (1) Adenocarcinoma of the uterus; (2) metastatic carcinoma of iliac nodes, posterior uterine wall, pouch of Douglas, omentum, rectum, bladder and liver; (3) perforation of rectum; (4) peritonitis





Fig. 1.—Low power photomicrograph ( $\times 200$ ) showing mass of tumor cells invading muscularis.

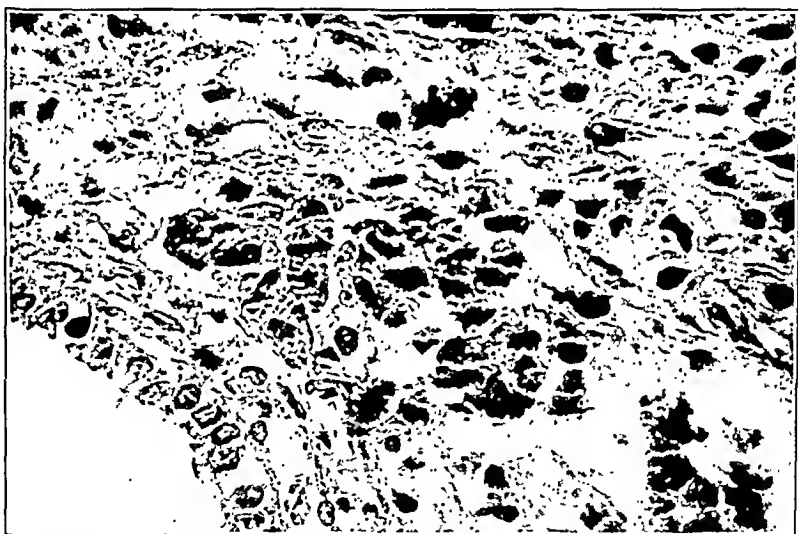


Fig. 2.—High power photomicrograph ( $\times 800$ ) showing anaplastic characteristics of tumor cells.

(*B. coli*); (5) thrombosis of iliac veins; (6) myofibrosis cardiac; (7) pulmonary congestion and edema; (8) congestion of liver and spleen; (9) bilateral chronic salpingitis; (10) diverticulosis coli; (11) renal calcification; and (12) hypertrophic bladder.

Only 5 proved cases of this type are reported in the literature. and one additional case with autopsy findings is here presented.

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## RECTAL ADMINISTRATION OF EVIPAL SOLUBLE IN OBSTETRICS\*

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IN JUNE, 1936, Gwathmey reported 150 cases in which he had administered evipal soluble rectally as a preanesthetic agent in general surgery.<sup>1</sup> Included within this report were the results of a series of animal experiments performed in the laboratories of the New York University School of Medicine which demonstrated that the therapeutic index (minimal lethal dose divided by the minimal anesthetic dose) for the rectal administration of the drug was 4. This offered an even greater margin of safety than the intravenous use of evipal soluble in which the therapeutic index was determined to be 3.3. The rectal administration of the drug produced satisfactory muscular relaxation and adequate length of action. Gwathmey concluded that the rectal administration of evipal soluble as a preanesthetic agent in surgery was safe, and that the dosage which he employed ("0.02 gram per pound body weight") made inhalation, local, or spinal anesthesia safer for the patient and easier for the doctor.

Evipal soluble has been employed intravenously in obstetrics as an anesthetic agent in both operative and spontaneous deliveries.<sup>2</sup> For general anesthesia in surgical procedures, evipal soluble has been given intravenously in over 800,000 cases in Europe alone.<sup>3</sup>

With the background of its successful use rectally and intravenously, it was decided to use evipal soluble rectally as an analgesic agent in obstetrics at this hospital and to evaluate the results. The drug was administered to 75 women in labor and records were kept of the results. Forty-one patients were primigravidas and 34 were multiparas. While the obstetric patients in this hospital average 35 per cent primigravidas and 65 per cent multiparas, many of the multiparous patients entered the hospital far advanced in labor and were unsuitable for the rectal use of evipal.

### ADMINISTRATION OF EVIPAL SOLUBLE RECTALLY

The technique of administering the drug is simple. First, the rectum is thoroughly emptied by a cleansing enema. The calculated amount of the solution is then injected into the rectum with a glass syringe, by means of a rubber urethral catheter inserted 4 to 6 inches into the rectum, and preferably above the presenting part. The solution is administered rapidly and is followed by the injection of 10 c.c. of water. The buttocks are pressed closely together for a few minutes and the patient is instructed to avoid straining. In only two instances was there any difficulty in retaining the solution, and in no case was there any evidence of rectal irritation.

\*The patients comprising this series were observed in the Los Angeles County General Hospital.

The total dosage employed varied between 1 and 4 gm. per patient. Although most of the women were given 2 gm. of evipal, some of the heavier patients received 3 gm. A second dose of evipal was administered to a few patients. Forty-nine out of the 75 women in the series received no other analgesic drug; 5 received 0.25 gr. of morphine sulfate, and 13 were given  $\frac{1}{32}$  gr. of dilaudid thirty to forty-five minutes before the use of the evipal solution. In 5 cases the desired results were not obtained by the use of evipal rectally, and its use was supplemented by the oral administration of pentobarbital sodium. One patient was given 20 c.c. of paraldehyde and 2 were given Gwaltmey rectal analgesia in addition to the rectal evipal. As a general rule we gave the rectal evipal when the cervix was dilated 2 to 4 cm. and regular uterine contractions, occurring every three to five minutes and lasting thirty to forty-five seconds, were present. In some instances the drug was given considerably later in labor.

#### GENERAL EFFECTS FOLLOWING RECTAL INSTILLATION

The effect following the use of evipal rectally was found to be variable. Within a few minutes all patients noted more or less drowsiness. Many slept for from thirty minutes to one hour. During this sleep the respirations were slightly shallow but were unchanged in rate. The pulse remained full and regular and there was no remarkable change in rate, although in most cases a slight increase was noticed. In a few cases flushing of the skin was observed. Blood pressure readings showed no significant alteration.

Uterine contractions were not affected in intensity or frequency, and in the series there was no increase in our usual number of operative deliveries. The average length of labor was 17.3 hours. Considering the number of primiparas, this figure is close to the average length of labor generally observed in this hospital. Contraction of the uterus following delivery is not affected and no unusual bleeding occurred in this series.

The length of effective analgesia proved extremely variable. In one case the effect lasted only fifteen minutes, the patient awakening at the end of that time alert

#### STATISTICAL DATA

Number of patients in series	75	
Primiparas	41	54.6%
Multiparas	34	45.4%

#### *Dosage of Evipal Soluble Rectal*

Smallest total dose	1 gm.	
Largest total dose	4 gm.	
Patients receiving one dose only	66	88%
Patients receiving two doses	9	12%
Patients receiving more than two doses	0	0

#### *Supplementary Drugs Employed*

Evipal used alone	49	65.4%
Morphine sulfate and evipal	5	6.7%
Dilaudid and evipal	13	17.3%
Pentobarbital sodium and evipal	5	6.7%
Gwaltmey rectal analgesia and evipal	2	2.6%
Paraldehyde and evipal	1	1.3%

#### *Length of Analgesia*

Shortest analgesia observed	15 minutes
Longest analgesia observed	6 hours
Average length of analgesia	2 to 2.5 hours

#### *Evaluation of Analgesia Secured*

Good results	35	46.6%
Fair results	22	29.4%
Poor results	18	24%
Cooperative patients	44	58.6%
Uncooperative patients	31	41.4%

In spite of a swinging fever, the white cell count was only 8,000 with 17 per cent stab forms. Sixty grains of sulfanilamide were administered daily for four days, then discontinued for a few days because of a sulphhemoglobinemia.

On September 30 (one month from term) the membranes ruptured spontaneously and labor began. Dilaudid and scopolamine were used for analgesia, and after four hours of labor, a living female child weighing 4 pounds and 13 ounces was delivered by low forceps. A blood culture was immediately taken from the umbilical cord, and no growth was reported after ten days.

During the puerperium the fever continued, now rising to 104° F. daily and becoming more sustained. Only two petechiae were noted throughout the entire illness, although they were constantly searched for. Although blood cultures continued to show the presence of virulent streptococci, no evidence of pelvic infection developed. Sulfanilamide was resumed in large daily dosages, one injection of polyvalent antistreptococcus serum was given, morphine and barbiturates were used freely, but none of the medication used appeared to have any favorable influence on the course of the disease.

The urine showed increasing amounts of albumin, and large numbers of red blood cells and casts. Repeated blood counts differed but slightly from the previous findings. The spleen or liver did not become palpable. Signs of cardiac failure appeared early, and the pulmonary congestion increased. Signs of pneumonia (or infarction?) appeared on the nineteenth post-partum day. She became irrational, deeply cyanotic, and died on November 1, one month after delivery. An autopsy was not granted.

The infant gained well and was in excellent health, but at the age of seven months died from an attack of acute enteritis.

#### DISCUSSION

When subacute bacterial endocarditis complicates pregnancy, it is very frequently mistaken for pyelitis until blood cultures or beginning cardiac failure direct attention to the true diagnosis. In those cases following abortion or delivery, it is often mistaken for puerperal sepsis. With any febrile disease in the presence of rheumatic heart disease or even with the history of chorea or rheumatic fever, bacterial endocarditis must be considered, and the differential diagnosis may be readily made in most instances as soon as it is taken under consideration.

Pregnancy cannot be considered to be of any etiologic importance in the development of bacterial endocarditis, nor can it be looked upon as conferring any sort of immunity in spite of the rarity of the association. Pregnancy does, however, seem to hasten the progress of the disease, probably because of the markedly increased cardiac output which begins early in gestation, and because of the circulatory burden associated with delivery or operative intervention.

It is most remarkable, however, that out of 12 viable infants born, 10 survived and were in good health. The 2 infant deaths, moreover, were unrelated to the maternal infection, one dying of prematurity and the other being stillborn as a result of premature separation of the placenta. In two of the surviving babies, blood cultures were positive for the *Streptococcus viridans* (showing that the placenta is not a barrier to the organism), but the cultures quickly became negative. Felsen and his co-workers<sup>11</sup> showed that in their case the immune titer of the infant's blood was as high as that of the mother, and this fact must be of importance in explaining the ease with which these babies overcome their bacteriemia.

11, 1936 at 7:47 P.M. She had had adequate prenatal care at a local clinic. Mild edema of ankles was present for two weeks.

*Findings on Admission.*—Blood pressure, 130/76; temperature, 99.4° F.; pulse, 94/min.; respiration, 20/min. Examination of heart and lungs essentially normal. Mild uterine contractions present every five minutes. Height of fundus 36 cm. Pelvic measurements ample. Position L.O.A. Station -2 cm. Cervix effaced 40 per cent and dilated 1 cm. Fetal heart tones 148, regular. Urine negative for albumin and sugar.

*Progress.*—10:00 P.M.: Mild uterine contractions every three minutes. Fetal heart tones 148. Station plus 1. Dilaudid,  $\frac{1}{32}$  gr., by hypodermic given at this time. Dilatation cervix 3 to 4 cm.

10:35 P.M.: Two grams of evipal soluble given rectally.

12:00 midnight. Dilatation of cervix complete and head on perineum. At 12:30 A.M. the patient was placed on the delivery table. 50 c.c. of  $\frac{1}{2}$  per cent novocaine was infiltrated into the perineum and a left mediolateral episiotomy was done. The patient was then anesthetized, using a total of 3 ounces of ether by drop method, and an easy prophylactic low forceps operation was performed. An 8 pound 7 ounce infant was delivered which was moderately asphyxiated, necessitating tracheal insufflation for a few minutes.

Following delivery, the ether mask was removed. The color of the patient was good and respirations were regular. The patient began to move and seemed to be awakening. The perineal repair had just been started when sudden cyanosis and cessation of respiration was noticed. Traction on the tongue was applied with an Allis clamp and artificial respiration and carbogen were given. Respirations returned after three to five minutes and cyanosis disappeared. Further recovery of the patient was uneventful.

#### EFFECT ON BABY

The fetal heart rate was not materially affected in any of our cases. Fifty babies in this series cried spontaneously. A delayed cry was noticed in 23 instances. Two babies were stillborn; in 1 case the fetal heart tones had not been heard during labor, while in the other a tentorial tear resulted from a difficult operative delivery. Mild asphyxia in which the babies were resuscitated with no difficulty was noted 17 times. Moderate fetal asphyxia was observed in 7 instances. Three of these mothers had received evipal and dilaudid, 1 had received pentobarbital sodium following evipal, and 3 had received evipal alone. Severe asphyxia in which the babies were resuscitated with difficulty by use of the tracheal catheter was noticed 3 times. Two of these patients had received evipal as the only analgesic agent, while the other had received evipal and dilaudid. The nurses in care of the nursery reported an exaggerated drowsiness of all of the babies in this series during the first day of life.

Babies with spontaneous cry	50	66.7%
Babies with delayed cry	23	30.7%
Babies stillborn	2	2.6%
Mild Asphyxia	17	22.6%
Evipal alone used	10	
Evipal and dilaudid	1	
Evipal and pentobarbital sodium	3	
Moderate Asphyxia	7	9.3%
Evipal alone used	3	
Evipal and dilaudid	3	
Evipal and pentobarbital sodium	1	
Severe Asphyxia	3	4.0%
Evipal alone used	2	
Evipal and dilaudid	1	

#### SUMMARY

1. Evipal soluble was administered rectally to 75 women in labor and the results were tabulated. The dosage corresponds to that of previous investigators.

and complaining to such an extent that it was necessary to use other drugs for the relief of pain. In a few cases relief from pain was secured for from four to six hours; but in general the effect of the drug lasted for two to two and one-half hours. Because of the short duration of effective analgesia by the use of evipal, our best results were obtained in those patients in whom delivery followed within two hours after administration of the drug. Forty-four of the 75 patients were considered reasonably cooperative on the delivery table, while 31 were not. Of this latter group many were wild and completely uncooperative. In 35 instances the analgesia secured was good, in 22 it was considered fair, while in 18 it was considered poor. The amount of amnesia as determined by questioning the patient on the first postpartum day also showed great variation, some patients remembering nothing, others having no amnesia whatsoever. The impression of the authors, and of the interns and nurses who observed these 75 patients, was that the patients were not securing as much relief from pain as was obtained by patients receiving other analgesic agents.

#### REACTIONS NOTED

*Minor Reactions.*—In several instances twitching of localized muscle groups was noticed. The upper or lower extremities were usually involved and occasionally the muscles of the face. These were rarely severe. In one case, however, generalized twittings of all the body muscles were present, severe enough to resemble a convulsion. In another case they resembled a chill. These reactions were of short duration and were not the cause of concern. As the patients dropped off to sleep, they disappeared. The above mild reactions have been generally described in the literature on evipal soluble.

*Severe Reactions.*—Two patients suffered severe reactions which were the cause of extreme concern. These cases are described in detail.

**CASE 1.**—(532-895.) White, female, aged 24, para ii, gravida iii. Last menstrual period March 15, 1936. Due Dec. 22, 1936. She was admitted to the hospital on Jan. 6, 1937 at 12:30 P.M. She had had two previous full-term pregnancies with spontaneous delivery of 8½ and 9 pound living babies. She had had no prenatal care. Pregnancy was uneventful to full term. Pains began six hours before admittance.

*Findings on Admission.*—Blood pressure, 132/76; temperature, 98.4° F.; pulse, 80/min.; respiration, 20/min. Examination of heart and lungs essentially normal. There were mild uterine contractions every twenty minutes. Height of fundus, 35 cm. Pelvic measurements were ample. Position L.O.A. Station floating. Cervix uneffaced and dilated 1 cm. Fetal heart tones 136, regular and strong.

Examination of urine was negative for albumin and sugar. Hemoglobin was 13.2 gm. (Sahli).

*Progress.*—9:00 P.M.: Moderate uterine contractions every ten minutes. Fetal heart tones were 136. Station plus 1. Dilation of cervix 4 cm. Effacement 50 per cent. Two grams of evipal soluble were given rectally at this time.

10:30 P.M.: Dilatation of cervix complete and head on perineum.

The patient was placed on the delivery table and was given 2 ounces of ether by drop method in order to permit draping and to prevent a precipitate delivery. Sudden cyanosis and a drop in respirations to 4 per minute was noticed. The ether mask was removed and carbogen given. The patient was comatose. She was given adrenalin (1-1,000) minims iii, 7½ gr. of caffein-sodio-benzoate, and 1 ampoule of coramine, by hypodermic. The blood pressure was 140/90, pulse rate 100. The skin was cold and clammy. Hot blankets were applied.

At 11:45 P.M., or approximately one hour after the above collapse, the patient regained consciousness. The respiratory rate was then 40/min. Fetal heart tones were 160/min. and regular in rate. Uterine contractions returned, and forty-five minutes later, at 12:15 A.M. a 7 pound 7 ounce baby was delivered spontaneously. No fetal asphyxia was present.

The third stage and further recovery of the patient were uneventful.

**CASE 2.**—(524-868.) White, female, aged 24, para 0, gravida i. Last menstrual period Jan. 29, 1936. Due Nov. 5, 1936. She was admitted to the hospital on Nov.

sinusitis and bilateral mastoiditis with more involvement on the left. A left mastoidectomy was performed at once by Dr. G. B. Tribbe. Following the operation, the patient was given 20 c.c. of prontosil intramuscularly every four hours, a total of 120 c.c. a day. She was also given a transfusion and progesterone, one international unit twice a day, to prevent labor. After two days her condition improved somewhat and the prontosil was cut to 15 c.c. every four hours which she continued to receive for three more days.

Following this therapy, the infection rapidly subsided. Her temperature remained normal after the fifth day. Labor began on Jan. 2, 1939, and she was delivered of a normal full-term infant, weighing 6 pounds, 9 ounces after a four-hour labor. The puerperium was uneventful and she was discharged on Jan. 14, 1939.

There are many cases in which an intercurrent infection may threaten the life of the parturient woman. We feel that in these cases the use of sulfanilamide and its derivatives is justified regardless of the effect on the fetus. Such a case has been presented and many similar cases will probably arise. The use of sulfapyridine in pneumonia during pregnancy offers possibilities of lowering a mortality rate that has varied little in the last decade. Until it is proved that these products are definitely injurious to the fetus, we feel that they should be used whenever indicated if the life of the mother is threatened.

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## COMBINED INTRA- AND EXTRAUTERINE PREGNANCY

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**C**OEXISTING intrauterine and extrauterine pregnancy is not an unusually rare condition. Up until 1913 there were collected and reported 243 cases of combined pregnancies. In 1926 Novak had added 32 more cases, and in 1935 Hefferman summarized the literature, reporting 2 more cases totaling 277. I found 9 additional cases in the recent literature bringing the approximate total of these cases to 286.

The greater number of cases reported did not terminate with a living child, as in the present instance. Uterine abortion before the fourth month usually occurred. A large number of the histories indicated multiple pregnancies in the families.

### CASE REPORT

Mrs. R. B., white, aged 28, para i, gravida 0, was seen in consultation on Sept. 3, 1938, complaining of severe lower abdominal cramps associated with spotting of several days' duration. Her past history was essentially negative. There were no previous pregnancies or history of miscarriage. The family history indicated multiple pregnancies. Menstrual history showed a regularity of menses up until July 15, 1938, which was her last menstrual period until the present spotting had appeared. Examination disclosed a healthy appearing woman, not acutely ill, merely complaining of cramplike pains in the lower abdomen. The latter was tender to palpation, with muscular rigidity on the right side. Vaginal examination showed a soft cervix and a brownish bloody discharge. The uterus was slightly increased in size, suggesting an early pregnancy. The right fornix presented a bulbous cystic mass the size of a lemon, intimately connected with the uterus and very tender. A diagnosis of ruptured right tubal pregnancy was made. At operation there were free blood in the peritoneal cavity and large blood clots over the fimbriated end of the bulbous, bluish tube. The uterus was slightly enlarged commensurate with such an early pregnancy. The right tube and appendix were removed. The peritoneal cavity was cleared of all free blood clots and the abdomen closed without drainage. The patient's postoperative course was very mild and she left the hospital on Sept. 14, 1938.

*Pathologic Report.*—Specimen consisted of an appendix, a Fallopian tube and a mass of blood clot. The Fallopian tube showed delicate fimbriae. The wall was

2. The analgesia and amnesia secured were extremely variable. The duration of analgesia was generally short, ranging from fifteen minutes to six hours, averaging about two and one-half hours. In some cases amnesia was complete and in others totally absent. Despite the fact that about 35 per cent of the patients received supplementary drugs, the total number of good results was low (46.6 per cent).

3. Two grave maternal reactions were observed. Although both patients recovered, the reactions were very alarming. These two cases are described in detail.

4. Three babies were moderately asphyxiated at birth when evipal was the only analgesic drug used during labor. Two babies in cases in which evipal alone was used during labor exhibited severe asphyxia. All the babies in this series were drowsy for about twenty-four hours following delivery.

#### CONCLUSION

We believe that evipal soluble in the dosage used is unsuitable for rectal administration as an obstetric analgesic agent.

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## MASSIVE DOSES OF SULFANILAMIDE IN PREGNANCY

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THE rapid acceptance of sulfanilamide and its derivatives in the treatment of many types of infection has resulted in a very incomplete literature on many phases of its use. The uses of and contraindications to the drug during pregnancy are one of the phases on which there is very little available literature. Recently Adair has published some experimental work on animals which indicated that the drug has definitely harmful effects on the fetus. And yet occasions will arise when the life of the fetus must be a secondary consideration, and the use of the drug a life-saving measure for the mother. We have encountered such a case, and used massive doses of the drug. We herewith report this case that it may serve as a guide in practically an uncharted field.

Mrs. L. H., para 0, gravida i, white, aged 24 years, was first seen by us on June 21, 1938, in the third month of her pregnancy. Last period March 19, 1938. Physical examination at this time was essentially negative. Pelvic measurements were ample. Kalin test was negative, and the blood count was within normal limits. Her pregnancy was uneventful except for an attack of acute left kidney pain. Pyelogram revealed a double ureter with hydronephrosis on the left.

On or about Nov. 1, 1938, the patient contracted an acute upper respiratory infection which rapidly developed into a paranasitis. She was given local treatment and sulfanilamide by mouth without any apparent benefit. On December 1 she developed bilateral otitis media, and both drums perforated. On December 10 she developed left mastoid tenderness and was admitted to George Washington University Hospital. An x-ray taken on admission showed left maxillary and ethmoid



# Society Transactions

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## CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF MAY 19, 1939*

The following papers were presented: **The Electrical and Mechanical Activity of the Human Nonpregnant Uterus.** Drs. Edmund Jacobson, Julius E. Lackner and Melvin B. Sinykin (by invitation). (For original article, see page 1008.)

**Pelvic Prognosis on the Basis of Recent X-ray Studies of the Female Pelvis.** Dr. Everett C. Hartley (by invitation). (For original article, see page 1037.)

**Estrin and Progesterone Relationship in Obstetrics and Gynecology.** Dr. Phillip F. Schneider (by invitation).

**The Clinical Use of Gonadotropic Hormone from Pregnant Mare Serum.** Drs. Carl P. Huber (by invitation) and M. Edward Davis.

**Postoperative Ureteral Obstruction Due to Ptosis of the Kidney.** Drs. M. L. Leventhal and E. M. Solomon. (For original article, see page 1061.)

**Velamentous Insertion of Cord with Spontaneous Rupture of Vasa Previa in Twin Pregnancy.** Drs. A. J. Kobak and M. R. Cohen. (For original article, see page 1063.)

**Tubal Pregnancy with Tuberculous Salpingitis.** Dr. I. F. Stein. (For original article, see page 1068.)

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## BROOKLYN GYNECOLOGICAL SOCIETY

*MEETING OF APRIL 14, 1939*

The following program was presented:

**A Case of Superfetation in Uterus Didelphys.** Dr. Irving T. Soifer.

**Studies in Artificial Ovulation With the Hormone of Pregnant Mares' Serum.** Dr. Samuel L. Siegler and Dr. M. J. Fein. (For original article, see page 1021.)

*MEETING OF MAY 5, 1939*

The following papers were presented:

**Introductory Remarks on the Brooklyn Maternal Mortality for the Year 1938.** Dr. M. V. Armstrong.

**Mortality in Cesarean Sections.** Dr. Frank P. Light.

**Anesthetic Deaths in Obstetrics: The Preventable Factors.** Dr. A. H. Rosenthal.

**Indications for Obstetrical Consultation.** Dr. H. S. Acken, Jr.

**Preventability and Treatment of Hemorrhage in Obstetrics.** Dr. J. A. O'Leary.

ruptured near the uterine extremity and the adjacent structures were heavily infiltrated with blood. The muscular wall of the tube showed evidence of recent hemorrhage, in areas there were bits of decidual tissue. There were a number of well-preserved immature chorionic villi which lay within a mass of blood clots.

Two weeks after leaving the hospital, Mrs. R. B. came to the office for examination. At this time her general health was very good except for a complaint of slight morning nausea. Examination disclosed a symmetrically enlarged uterus of about ten weeks' pregnancy which aroused a suspicion of a coexisting uterine pregnancy. This was verified on Oct. 1, 1938 by a positive Asehlheim-Zondek reaction.

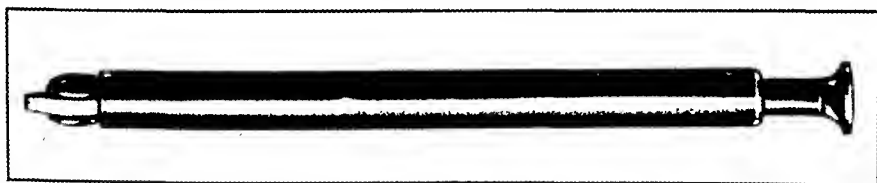
The course of pregnancy was entirely normal, and on May 2, 1939 this patient was delivered of a normal, living, female child.

619 SOUTH BONNIE BRAE STREET

## AN INSTRUMENT FOR THE TREATMENT OF TRICHOMONAS VAGINITIS

MILTON ROBINSON, M.D., NEW YORK, N. Y.

IN THE treatment of *Trichomonas vaginalis* vaginitis, as well as in other types of leucorrhea, or vaginitis, the medication prescribed has been compounded into tablets, capsules, or pessaries. The method of introducing these substances into the vagina has been left to the ability of the physician to teach the patient the proper technique and to the ingenuity and physical skill of the patient to follow it. For esthetic reasons many women find the introduction of medication with their fingers into the vaginal tract unpleasant. This is especially so in virgins and nullipara with small introitus. For aseptic reasons one can see that in the attempt to place the medication properly with the finger the tissues may be readily traumatized and infected with organisms which, if not already there, might be introduced by the fingers.



Since it is not always feasible to have the patient return to the office each time for treatment, I have devised a small apparatus, no thicker than the average douche nozzle, seven inches long, of a nonmetallic substance which will grasp any solid form of medication and can be easily introduced into the vagina. The tablet is thus placed high up in the vault, in approximation to the cervix. When this medication has been introduced into the proper place, a spring release is pressed and the instrument is withdrawn. The substance is left in the vagina to mix intimately with the vaginal and cervical secretion, to dissolve, and by gravity flow over the vaginal walls. The instrument will resist all of the commonly used cold sterilizing solutions (lysol, bichloride, alcohol) and can be used repeatedly over a long period of time without impairing its effectiveness.

The instrument is manufactured by the J. Kriser Corporation, 30 East Tenth St., N. Y.

segment and the lifting of the bladder connected with this, and (2) the lowering of the fetal head. This explains why, between the seventh and tenth months of pregnancy, the distance becomes constantly smaller so that during the last weeks of pregnancy the outline of the head almost touches the shadow of the bladder. However, if a body is interposed between the fetal head and the uterine wall, such as for instance the placenta or a myoma, the distance is in excess of 1 cm. The authors made this test on 30 pregnant women. In 16 of them hemorrhages had occurred during the second half of pregnancy and the other 14 cases served as controls. They found that this roentgenologic method permits the detection or exclusion of a placenta previa if it is of the central or lateral type. A placenta previa marginalis, particularly if located on the posterior uterine wall, usually cannot be determined in this manner. Another disadvantage is that the method can be used only if the fetus is in the vertex position. However, the authors suggest that in some cases of oblique, transverse or pelvic position, external version into the vertex position can be tried. They succeeded in accomplishing this in three cases.

J. P. GREENHILL.

Lloyd, O., and Giesen, J. E.: *The Treatment of Placenta Praevia*, Brit. M. J. 1: 1258, 1938.

At Queen Charlotte's Maternity Hospital a standardized method for treatment of placenta previa is established. A series of 143 cases treated in the past five years is compared with a similar number treated prior to this period. The principles of the treatment consist of (1) proper preparation for examination of the patient per vaginam. This includes blood grouping and preparations for transfusion and for vaginal packing. (2) Vaginal examination under light general anesthesia. A diagnosis was established as to the type of placenta previa present, central, marginal, or lateral.

The central placenta previa was treated by routine cesarean section irrespective of the condition of the fetus. If bleeding follows the vaginal examination, vagina and cervical canal are packed. The patient was given morphine and transfusion prior to operation.

Lateral and marginal placenta previas were treated by simple rupture of the membranes and plugging of the vagina where bleeding ensued. In all cases, blood loss was replaced by early and adequate transfusion.

Podalic version is not advocated, but where a complete breech presentation was present and the os sufficiently dilated, a leg was pulled down to effect pressure by the half breech. Willett's scalp forceps were employed on one or two cases after removal of the packing. Stress is laid on efficient packing of the vagina.

The advantages claimed for packing are that bleeding can be completely arrested, and time gained to restore the patient's general condition; vascular sinuses exposed by placental separation are compressed and clotting can occur; packing of the vagina in conjunction with artificial rupture, though a stimulus to uterine contractions, does not result in unduly rapid delivery.

The results of this treatment show a mortality rate of 1.4 per cent, a morbidity rate of 15.4 per cent, and a stillbirth rate of 53.8 per cent, as compared with the group of 143 patients treated prior to this standard method with a mortality rate of 5.6 per cent, morbidity rate of 14.7 per cent, and stillbirth rate of 50.05 per cent.

Emphasis is laid upon the value of a predetermined routine.

F. L. ADAIR AND S. A. PEARL.

Liepert, M.: *The Best Form of Therapy for Placenta Previa*, Arch. f. Gynäk. 167: 52, 1938.

The incidence of placenta previa was 1.69 per cent at the Cologne Frauenklinik during the last decade. Of these cases, 128 were classified as low implantation, 47 as marginal, 102 as lateral, and 121 as central.

# Department of Reviews and Abstracts

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CONDUCTED BY HUGO EHRENFEST, M.D.

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## Selected Abstracts

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### Placenta

Loyonnet, R., and Ambre, E.: Severe Hemorrhage Due to Low Insertion of the Ovum in the Early Months of Pregnancy, *Rev. franç. de gynéc. et d'obst.* 33: 613, 1938.

In a series of 750 pregnancy cases in the Lyon Obstetric Clinic, the authors observed 5 cases of severe hemorrhage in the early months of pregnancy which were due to placenta previa and which necessitated evacuation of the uterus. The authors accept the explanation of Rhenter and Pageaud for this condition, namely that during the fourth month, after the decidua at the internal os is absorbed, chorionic villi become free and lead to bleeding. The treatment of choice in such cases is artificial rupture of the membranes. Usually this is not sufficient to start labor, and oxytocies must be administered. Other measures which may have to be employed are: cervical tamponade, a Champetier de Ribes bag or a Braxton Hicks version.

The prognosis for the mother in these cases is less serious than it is for placenta previa near or at term, but of course the fetus must be sacrificed.

J. P. GREENHILL.

Cetroni, M. P.: Placentography and Radiological Diagnosis of Placenta Previa, *Clin. obstet.* 39: 373, 1937.

The author summarizes the work already done on placentography. He points out that direct placentography, by injecting intravenously, opaque substance, is impractical since the dose required is lethal.

He states that there are two indirect methods of visualizing the placenta. The first he names "amniotography," which consists of injecting a contrasting liquid in the ovular cavity. The results obtained by this method seemed satisfactory to the author, because in addition to the visualization of the placenta, the contour of the fetus and the cord are also demonstrable. The second method is based on revealing the distance between the fetal head and the urinary bladder which is filled with a contrasting fluid. In cases of placenta previa, this distance is considerably greater.

AUGUST F. DARO.

Jablonski and Meisels: Diagnostic Value of Cystography in Placenta Praevia, *Zentralbl. f. Gynäk.* 62: 532, 1938.

Observations are reported with the cystographic method which Ude and Urner recommended for the diagnosis of placenta previa. The method is suited especially for the cases in which the fetus is in the vertex position. Ude and Urner maintained that the distance between the lower outline of the fetal cranium and the contrast-shadow of the bladder measures normally at the most 1 cm. and that this distance is taken up by the thickness of the wall of the urinary bladder, of the uterine wall, and of the fetal scalp. Jablonski and Meisels, however, assert that the distance is dependent on (1) the degree of dilatation of the lower uterine

If this conception is viewed in the light of quantitative disturbances in the physiologic function of the placenta, this theory is not different from other explanations.

In some cases of hyperemesis and toxemias during the early months of pregnancy, there are likewise very marked increases in the excretion of prolan. There is a possibility that the body can dispose of these excesses through the urine and cerebrospinal fluid. When, however, there is a retention of this excess in the tissues of the body, the disturbances which result are hydatid mole, abortion, or abruptio placentae. The cause of the premature separation of the placenta, especially of uteroplacental apoplexy, is a disturbance in the hormonal relationship between the placenta and the corpus luteum.

J. P. GREENHILL.

**Batzifalvy, J.:** Pathology and Surgical Treatment of Utero-Placental Apoplexy and Ablatio Placentae, *Arch. f. Gynäk.* 163: 552, 1937.

The author has collected the world statistics on ablatio placentae and uteroplacental apoplexy and presents his conclusions. The term "ablatio placentae" should be used for the milder cases of premature separation of the normally situated placenta and "uteroplacental apoplexy" for the severer forms of this condition. The frequency of uteroplacental apoplexy is difficult to determine since most authors have included the ablatio placentae figures in their reports. However, the frequency varies between 0.09 per cent and 1.06 per cent. There is no question that the uteroplacental apoplexy is a true pregnancy toxemia which can and frequently does result in fatal outcome to mother and child. It resembles other forms of toxemia and differs only in the location of the pathology which results. Such changes are found in the decidua, placenta, uterine wall, and uterine vessels.

The symptoms depend on this location and upon the extent of the resultant hemorrhage and the diagnosis and prognosis often depend on the extent of the placental separation, the latter also on the anatomic changes produced in the uterus, and the severity of the accompanying toxemia. The mortality ranges from 5, 10, 15, and 60 per cent.

Treatment should be obstetric for partial separation and "surgical" for complete separation. These latter methods and the results obtained are as follows: (1) vaginal cesarean section with a mortality of 45.4 per cent, (2) abdominal cesarean section, which should be the method of choice, with a mortality of 16.1 per cent, (3) precesarean hysterectomy, mortality 16.6 per cent, (4) uterine extirpation following cesarean section, mortality 35.3 per cent.

The results obtained can be definitely improved by early and accurate diagnosis followed by immediate appropriate treatment. If the uterine wall is normal and not involved the best treatment is conservative. Cesarean section should be done if there is hemorrhage into the uterine wall and the patient is in good condition. The uterus may be conserved only if this organ contracts readily, otherwise it must be removed. In the latter more severe type of case the risk is great but can be materially reduced by the use of frequent and early blood transfusions.

RALPH A. REIS.

**Trillat, P., and Magnin, P.:** Statistical and Critical Study of Retroplacental Hemorrhage Observed in 20,000 Labor Cases, *Rev. franç. de gynéc. et d'obst.* 33: 901, 1938.

In a series of 20,000 labor cases observed at the Lyon Midwives School, there were 66 instances of retroplacental hemorrhage. There were three forms, a mild type with survival of the infant (20 cases), a moderate type with fetal death but without serious consequences for the mother (42 cases) and a grave type, commonly known as the Couvelaire type with fetal death and serious prognosis for the mother (four cases).

Following medical stimulation of labor pains, 89 patients were delivered spontaneously, and 19 were treated by simple rupture of the membranes. Braxton Hicks version was done in 24 and version and extraction in 37. In 18 of the latter, craniotomy was performed on the aftercoming head. Of the 40 patients in whom bags were used, 24 were followed by spontaneous delivery and 16 by version and extraction. The remaining 182 were terminated by cesarean section.

The fetal mortality following cesarean section was 21.5 per cent and the maternal mortality was 6.25 per cent. For the entire series, the fetal mortality was 33.25 per cent and the maternal mortality 6.4 per cent.

The author concludes from his studies that every patient should have a careful vaginal examination for the exact diagnosis of the type of placenta previa and that the examiner must be prepared to terminate immediately the pregnancy if hemorrhage ensues. He recommends Braxton Hicks version as the treatment of choice when the fetus is nonviable or dead. For all other patients cesarean section is the safest for both mother and baby. He believes that each patient must be individualized as so many factors such as parity, severity of the hemorrhage, viability of the fetus, etc., play a role. The general principle involved is to save the mother and if possible, to rescue the fetus.

RALPH A. REIS.

Nankivell, J. W.: Expulsion of a Placenta Praevia in Advance of the Foetus, Brit. M. J. 2: 527, 1937.

The case history is given of a multipara in whom two initial hemorrhages were followed several weeks later by the expulsion of the placenta two hours before the birth of the infant.

The literature contains only four references to similar expulsion of a placenta previa in advance of the fetus.

There was no extraordinary blood loss preceding or following expulsion in the case quoted.

F. L. ADAIR AND S. A. PEARL.

Lim, K. T.: A Comparative Study of 93 Cases of Placenta Praevia and 74 Cases of Abruptio Placentae, Chinese M. J. 53: 109, 1938.

The author reports 93 cases of placenta previa and 74 cases of abruptio placentae observed in 5,220 deliveries, during the last 14 years, in the Peiping Union Medical College.

Over 70 per cent of both types of cases were admitted to the hospital as emergency without any antenatal care, and a large number of them were critically ill and potentially infected.

Reduction of maternal and fetal mortalities depends on: The early hospitalization of these cases; not hastening delivery regardless of the general condition of the patient, and more liberal use of prophylactic transfusions.

C. O. MALAND.

Heim, K.: The Pathogenesis of Abruptio Placentae, Monatschr. f. Geburtsh. u. Gynäk. 104: 1, 1936.

The author found a definite relationship between hyperprolauria and pathologic conditions in pregnancy. Next to hydatid mole, the greatest output of prolaur in the urine is to be found in cases of abruptio placentae, especially those cases designated as uteroplacental apoplexy. Likewise in eclampsia there is a great increase in prolaur in the blood, in the cerebrospinal fluid and in the placenta. Hence, in the opinion of the author, abruptio placentae, pre-eclampsia, and eclampsia are dysharmonic toxemias of different symptomatology but of the same etiology.

Since the prognosis for the mother may be considered practically hopeless, while the outlook for the fetus is excellent, it is apparent that a conservative attitude should be taken toward the pregnancy in an effort to obtain a viable infant. In the reported cases where the pregnancy proceeded to term or near term and a spontaneous delivery occurred, the average length of life following delivery was twelve weeks. In those cases where operative intervention was made or where spontaneous abortion occurred, the average length of life was six weeks post partum, showing that there is no advantage to the mother in either therapeutic abortion or operative delivery. Kobacker's<sup>4</sup> case in which a normal surviving infant was obtained by cesarean section on a moribund mother justifies this procedure or the performance of a post-mortem cesarean, but with this exception the obstetrician would do well to allow a spontaneous onset of labor.

Although sulfanilamide was used in Case 3 without apparent effect, Major and Leger<sup>13</sup> have recently reported the cure of a well-authenticated case of *Streptococcus viridans* endocarditis following the administration of sulfanilamide in large doses. Such a report would warrant the continued use of this drug.

It is also noteworthy that although streptococci are present in the blood, a localized pelvic sepsis does not occur during the puerperium, probably because of the patient's resistance to the organism. Were it not for the persistent focus on the heart valves, the septicemia might easily be overcome. In spite of the absence of uterine sepsis, the lochia has been shown to contain the streptococcus, and it need not be pointed out that the presence of such a patient on a maternity ward is hazardous, for the viridans organism has been known to produce puerperal sepsis of epidemic proportions.

#### SUMMARY

There have been 15 proved cases of *Streptococcus viridans* endocarditis reported in pregnancy, to which we have added 3 case reports. The disease may be easily mistaken for pyelonephritis or puerperal sepsis at the onset but is readily differentiated by culture of the blood, examination of the heart, and careful search for embolic phenomena. While all of the mothers have died, 10 out of 12 viable infants born have survived. Transient bacteremias in the fetus have been noted twice, but the infection is easily overcome. Interference with the pregnancy or operative delivery is not advisable, and efforts should be made to carry the fetus to viability.

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Among the 66 cases were 34 instances without albuminuria. These cases were milder than those associated with the toxemias of pregnancy. This series of cases verified the belief that retroplacental hemorrhage is more serious and more frequent in multiparas and among women past 30 years of age. The total fetal mortality in this series was 70 per cent. There were only 2 maternal deaths and these occurred in the series of the four severe cases.

All of the patients were treated by artificial rupture of the membranes. The authors never resorted to surgical treatment.

J. P. GREENHILL.

Mahon, R.: Two Cases of Normal Labor After Preceding Severe Uterine Apoplexy, *Bull. Soc. d'obst. et de gynec.* 27: 700, 1938.

The author reports two cases in which conservative cesarean section had been performed for grave uterine apoplexy and in which three and four years, respectively, after these operations, live children were born through the vagina. The author is not convinced that removal of the uterus improves the prognosis of uterine apoplexy. Among the 12 cases of severe uterine apoplexy observed and proved at laparotomy by Mahon the treatment was as follows: 5 conservative cesarean sections with 1 death, 5 cesarean sections followed by hysterectomy with 3 deaths, and 2 hysterectomies of unopened uteri with 1 death. The author favors conservative cesarean section because this operation saved 80 per cent of the mothers and retained their reproductive capacity, whereas hysterectomy saved only 50 per cent of the women and sacrificed their ability to have children. However, hysterectomy may have to be performed occasionally for intractable bleeding.

J. P. GREENHILL.

Currie, David: The Causes and Treatment of Retained Placenta, *Brit. M. J.* 2: 57, 1937.

Two types of retained placenta occur: one is simply a retained placenta, the other is adherent (placenta accreta or increta) which is very rare (1 in 6,000 to 1 in 4,000 births).

Retained placenta is characterized by a complete or partial separation of the placenta which is held in the upper segment of the uterus and gives rise to hemorrhage. The common cause of retention is atony or uterine inertia. Secondary causes may be a full urinary bladder or fibroids obstructing the passage.

In the presence of bleeding, manual removal must be prompt, though this is a method attended by a high morbidity and mortality.

A method for injecting the umbilical vein to effect separation and expulsion of the placenta is described. Sterile water may be used. In the Leeds Maternity Hospital, 186 cases had been injected; two ended fatally, and 8 were morbid. The incidence of manual removal dropped from 25 to 1 or 2 a year. The death rate in the former was 1.6 per cent as against 15.4 in the manual removal group, and the morbidity rate was 8 per cent as against 45.2 per cent. The method may be used in cases of post-partum hemorrhage and as a means of clearing the field before repair of episiotomy wounds or tears accompanying a difficult instrumental delivery.

F. L. ADAIR AND S. A. PEARL.

Tiemyeyer, A. C.: Placenta Accreta, *South. M. J.* 31: 608, 1938.

Two cases of placenta accreta are presented with a brief and concise analysis of the antecedents in the clinical history and the associated gross and microscopic pathologic changes. The incidence in the author's clinic was 1 in 4,312 deliveries.

As a result of an absence or a deficiency in the development of the decidua basalis, the placenta becomes organically attached to the uterine musculature,



thereby preventing the normal mechanism of separation of the placenta in the third stage of labor. There may be degrees of uteroplacental accretion from partial to complete, depending upon the area of the placental surface involved. Occasionally, placentas otherwise normally implanted may show mild evidences of the condition with attachment of a single cotyledon. Microscopically, the chorionic villi invade the musculature interdigitating with the fibers and bundles.

The first patient was 33 years of age and had 8 pregnancies in fourteen years, of which the seventh was complicated by prematurity, incomplete manual removal of a retained placenta necessitating subsequent curettage, hemorrhage, and puerperal sepsis with prolonged convalescence. She had the eighth spontaneous delivery in her home, and when the placenta failed to deliver two hours later, Credé expression was ineffectually attempted followed by a manual removal of several pieces of placenta with associated bleeding. The uterus was packed. In the hospital the uterus was explored and efforts to remove the placenta were prevented by inability to find a line of cleavage. Bleeding and shock necessitated packing. Following two transfusions and recovery from shock, supravaginal hysterectomy was performed with successful outcome.

The second patient was a 20-year-old primigravida in whose history the only deviations from normal were a scantiness of menstruation and inability to become pregnant in three years. The present gestation terminated prematurely at thirty weeks. After a third stage of two hours followed by an unsuccessful Credé maneuver and attempts at manual removal associated with hemorrhage the uterus was packed, a transfusion given, and supravaginal hysterectomy performed. Good recovery.

Placenta accreta is more common in multiparas than in primiparas. A history of previous manual removal of a placenta, sepsis, or curettage is significant. It has been suggested that disturbances of the corpus luteum may be an etiologic factor. Excessive erosive power of the trophoblastic villi, and insufficiency of antiferment production to check inordinate erosion have been suggested, but they do not explain the constant finding of a poorly developed decidua.

An important point in differential diagnosis between placenta accreta and placental incarceration as result of hourglass contraction of the uterus is found in the fact that in a case of placenta accreta there is no bleeding until attempts are made to remove it.

Manual attempts to separate the placenta and curettage are contraindicated. Shock and hemorrhage should be combated and supravaginal hysterectomy performed.

ARNOLD GOLDBERGER.

Irving, Frederick C., and Hertig, Arthur T.: *A Study of Placenta Accreta*, Surg. Gynec. Obst. 64: 178, 1937.

Eighteen clinical cases of placenta accreta are reported, and 86 others described in the literature are reviewed. The incidence in the clinic has been 1 case in every 1,956 deliveries.

The essential cause of this condition is partial or complete absence of the decidua basalis, so that the placenta is attached directly to the myometrium. In 12 of the cases the decidua vera was also examined and found to be normal in only 2 instances, thus indicating a generally defective development of the endometrium when the ovum was implanted.

Supravaginal hysterectomy with no attempt at manual extraction of the placenta yields excellent results, since of the 19 cases so treated, no mothers died. Attempt at manual extraction of the adherent placenta is extremely dangerous. Of the 30 cases in the combined series where this procedure was effected, 20 (66.6 per cent) died.

Transfusion should be employed in every case in which the blood loss exceeds, even by a small amount, the normal limit.

WILLIAM C. HENSKE.

King, Arthur G.: Placenta Accreta, Ohio State M. J. 34: 652, 1938.

Three cases of placenta accreta are presented bringing the total number of reported cases to 109. Two of these cases followed previous cesarean section and myomectomy with postoperative infection. The third was in a young para x whose last pregnancy terminated in an abortion. The treatment can be standardized on sound statistical evidence as: hysterectomy with no efforts at manual or instrumental removal of the placenta.

It is believed that placenta accreta is due to a mechanical, traumatic, or infectious insult to the endometrium combined with the chance that implantation will occur at the disturbed area. Endocrinopathy must be considered as a possible factor. Among the traumatic factors, serious consideration must be given to previous cesarean section, which was a likely etiologic factor in at least 6 per cent of all the reported cases. It is predicted that placenta accreta will become more common, particularly with the increased frequency of cesarean section.

The possibility of placenta accreta should be considered in any woman with a history of an endocrine disturbance, an abortion, or frequent pregnancies in rapid succession, and more particularly, a previous cesarean section. This possibility should militate against unnecessary abdominal deliveries, but might well bolster the argument for repetition of cesarean section.

J. P. GREENHILL.

Corinaldi, F.: Placental Abscess, Riv. ital. di ginec. 20: 180, 1937.

The author describes a case of placental abscess observed in a primipara, 25 years of age, after spontaneous birth of a seven months' live fetus. Both macroscopic and microscopic examinations revealed the abscess to have formed in the site of a thrombus. The cultures of the pus showed *Bacillus coli*. The author discusses the rarity and etiopathogenesis of this condition and demonstrates that the infection of the placenta was of hematogenous origin.

AUGUST F. DARO.

v. Pallos, K.: The Origin of Subchorial Cysts of the Placenta, Arch. f. Gynäk. 163: 63, 1936.

The author found gross subchorial cysts in 4.6 per cent of the 2,500 placentas examined. Following separation of chorion and amnion, the author was able to demonstrate subchorial cysts in 36.8 per cent with a hand lens. Microscopically, such cysts were demonstrable in every instance. The smallest cysts are by far the most common and are usually found in the outer third of the placenta. The large cysts are much less common and are found in the middle third of the placenta around the area where the larger placental vessels divide. These cysts arise most probably from basal ectoderm and are really trophoblastic. Degeneration of the cells of the trophoblast produces the cysts. Areas of necrosis are found surrounding the larger cysts; these are purely mechanical in origin and are due to pressure of the growing cysts on the cotyledons. These subchorial cysts are of interest embryologically and anatomically but have no clinical significance.

RALPH A. REIS.

Rhamy, B. W.: Chorioangiofibroma of the Placenta, J. Lab. & Clin. Med. 22: 899, 1937.

Chorioangiofibromas of the placenta are rare and presumably benign tumors. They vary in size from a grain of wheat to an apple, are sharply circumscribed and may be single or multiple. The author reports a case, the obstetric history of the patient being uneventful. The placenta was irregularly ovoid and contained 8 irregular, protruding, solid nodules which could be easily enucleated; they were covered by a fibrous capsule containing numerous blood vessels. Besides these eight protruding nodules, there were numerous smaller ones, varying

from 0.5 to 1.5 cm. in diameter, in the substance of the placenta. Microscopically, these tumors are separated from the placenta proper by a thick coat of compressed syncytium or Langhans's cells. The mass is composed of fibrous tissue containing capillaries of varying diameters lined with single layers of epithelium. The connective tissue is loosely areolar and consists of spider connective tissue cells. In the pinkish white areas, the connective tissue stroma is quite dense.

W. B. SERBIN

**Marchetti, Andrew A.: A Consideration of Certain Types of Benign Tumors of the Placenta, Surg. Gynec. Obst. 68: 733, 1939.**

Benign tumors of the placenta designated as chorioangiomas are relatively rare. On the basis of their histologic structure and pattern, these tumors are differentiated into several types: The cellular or immature, the vascular or more mature type, and that type accompanied by varying degrees of degenerative changes. These forms may intermingle in all gradations in the same tumor. The tissue originates from the chorionic mesenchyme, the proliferating endothelium and blood vessels playing the leading role, the stroma a subordinate or accessory role. Clinically chorioangiomas are of little significance.

WILLIAM C. HENSKEL

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## Item

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### **American Board of Obstetrics and Gynecology**

The written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 6, 1940, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held in June, 1940.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J., on June 8, 9, 10, and 11, 1940, immediately prior to the annual meeting of the American Medical Association in New York City.

Application for admission to Group A, Part II examinations must be on file in the Secretary's Office not later than March 15, 1940.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

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## MANAGEMENT OF BREECH DELIVERY IN MULTIPARAS

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THE subject of breech delivery in primiparas has been discussed in an article recently published,<sup>1</sup> and certain conclusions have been drawn from analysis of fifty years' experience with the management of this condition at the Boston Lying-in Hospital. It is of interest to present a survey of the concurrent breech deliveries in multiparas and to determine whether the conclusions drawn from the former series may be applied to the latter.

From 1888 to 1937 inclusive, among the 2,035 breech cases occurring, 560 deliveries by the pelvic route and 20 by abdominal cesarean section have been selected. All of the infants were born of multiparas at or near full term; all weighed 6 pounds or more at birth; and in all cases, except for the risks inherent in the birth process itself, the infants should have been born alive and well. Table I indicates the method of selection, the reasons for which have been discussed in previous articles.<sup>1, 2</sup> They need not be repeated here except to state that the cases eliminated from consideration have been so treated because of evident nonviability of the infant, or because of the added fetal risks inherent in prematurity, constitutional maternal conditions dangerous to the child in utero, and such unpredictable abnormalities as placenta previa, ablatio placentae, and frank prolapse of the cord.

The stillbirths and neonatal deaths in this series are classified in two groups: those of *mechanical* and those of *intercurrent* causation. Mechanical deaths are those due to asphyxia or trauma, demonstrable clinically or at post mortem. Intercurrent deaths result either from incidental pathology of early neonatal life presumably independent of the mechanism of the birth process, or from such purely extraneous circumstances as may be specified in each given case. This type of fatality is included in the statistics to be presented, since in certain instances the question of mechanical etiology cannot entirely be ruled out.

From Table I the evidence is clear that 8.2 per cent of the 560 infants delivered through the pelvis and 10 per cent of the 20 born by abdominal section failed to survive. On the other hand, as indicated in Table II, the fatality rate has fallen from 14.5 per cent in the first 88 deliveries beginning in 1913 to 4.5 per cent in the last 200 ending with 1937. When, moreover, the deliveries from 1888 through 1912 are added to those of the last quarter-century, the recent improvement in results becomes more clearly marked as represented in Fig. 1.

Table III summarizes the results of breech delivery per vias naturales, contrasting the stillbirth and neonatal death rates before and after March 1, 1921. In our previous article we discussed the change in service policy from "normal" or "assisted" breech delivery to routine extraction under full anesthesia during the second

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stage of labor, effective on the date mentioned, and outlined the reasons upon which this change of policy was based. It is of interest to note that in multiparas the stillbirth and neonatal death rate fell from 12.7 per cent before to 5.3 per cent after this date, in the case of single infants, and from 12.5 per cent to 5.1 per cent when multiple pregnancies are included. Since similar experience has led us to believe that routine extraction during the second stage is safer for the infant delivering by the breech of the primigravid woman than the classically recommended "normal" or "assisted" delivery, the above figures cannot but lead us to the same conclusion in the case of the multipara.

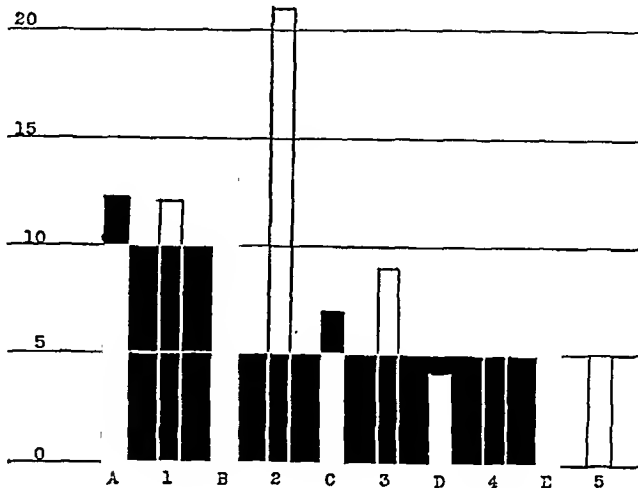


Fig. 1.—Mortality in breech delivery (1888-1937). Mature single infants. Multiparous deliveries in black and primiparous deliveries in white.

				MORT.
A.	1888-1911	104 Deliveries	13 Fatalities	12.5%
1.	1888-1905	82 Deliveries	10 Fatalities	12.2%
B.	1911-1921	100 Deliveries	13 Fatalities	13.0%
2.	1905-1920	100 Deliveries	21 Fatalities	21.0%
C.	1921-1927	100 Deliveries	7 Fatalities	7.0%
3.	1921-1928	100 Deliveries	9 Fatalities	9.0%
D.	1927-1932	100 Deliveries	4 Fatalities	4.0%
4.	1928-1932	100 Deliveries	5 Fatalities	5.0%
E.	1932-1937	100 Deliveries	5 Fatalities	5.0%
5.	1932-1937	100 Deliveries	5 Fatalities	5.0%

The 15 intercurrent deaths reported may be summarized as follows:

- |   |         |
|---|---------|
| 1. Intrauterine death during labor before admission to hospital | 4 cases |
| 2. Sudden death of infant,                                      |         |
| a. 24 hours post partum, ascribed to atelectasis                | 1 case  |
| b. 92 hours post partum, no cause assigned by autopsy           | 1 case  |
| 3. Neonatal death, ascribed to atelectasis                      | 1 case  |
| 4. Neonatal deaths, ascribed to congenital heart disease        | 3 cases |
| 5. Neonatal deaths, ascribed to hemorrhagic disease             | 3 cases |
| 6. Neonatal deaths, ascribed to bronchopneumonia                | 2 cases |

It should be stressed again that without definite post-mortem evidence to the contrary it cannot be said with complete assurance that the fatalities ascribed to atelectasis, congenital heart disease, hemorrhagic disease, or even bronchopneumonia might not, in some instances, have been caused by mechanical injury to the central nervous system at the time of birth.

The 31 mechanical deaths, summarized in Table IV, are classified into groups designed to point out the method of death.

- Progesterone, effect of crystalline corpus luteum hormone, on ovaries and related endocrine organs (Mazer and Israel), 625  
 metabolism and utilization of, given intramuscularly to women (Hamblen, Powell, and Cuyler), 557
- Progestin (poluton), synthetic, effect of ingested estrone (progynon DH) and parenterally administered, upon human castrate uterus (Neustaedter), 609
- Progynon-B injections (Geist and Salmon), 392
- Prolan, excretion of, in urine of abortion cases (Brown, Henry, and Venning), 927
- Prolapse of uterus, changes of urinary tract associated with (Wallingford), 489  
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- Psychoneurosis with exacerbation at time of menopause (Young), 115
- Psychoses, depressive, associated with menopause (Young), 116  
 organic, associated with menopause (Young), 116
- Ptosis of kidney, postoperative ureteral obstruction due to (Leventhal and Solomon), 1061
- Puerperal and postabortal infections, use of sulfanilamide in (Morris), 67  
 inversion, acute, of uterus, management of (Cosgrove), 912
- Puerperium, afterpains and painful engorgement in, treatment of, with testosterone propionate (Abarbanel), 1043  
 and pregnancy, relationship of estrogens and other placental hormones to sodium and potassium balance at end of (Taylor, Jr., Warner, and Welsh), 748  
 course of, in overweight primiparas, pregnancy and labor (Moller-Christensen), 365 (Abst.)  
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 streptococcal infections during, hemolytic, treatment of, and pregnancy with sulfanilamide and immunotransfusion (Chandler and Janeway), 187
- Purpura hemorrhagica, idiopathic, problem of, in pregnancy and neonatal period (Bernstein, Newman, and Hitzig), 323  
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- Radiation, influence of repeated, on salvage statistics of carcinoma of cervix (Scheffey), 907  
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- Rectal administration of evipal soluble in obstetrics (Roscnblum and Webb), 1075  
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- Rectovaginal septum, fibers of, of female pelvis (Power), 33
- Renal function tests in eclampsia (Chesley), 433
- Retrodisplacement, post-partum, value of knee-chest exercises in (Eichner), 488 (Abst.)
- Reviews and abstracts, department of, 178, 363, 550, 736, 1083
- Rheumatic heart disease, pregnant women with, circulation time studies in (Clahr, Greenstein, and Klein), 39
- Rotation, asymptomatic axial, of full-term uterus through 180 degrees (Hanley), 164
- Rupture of adrenal in newborn infant, hemorrhage and (Philipps), 182 (Abst.)  
 of membranes, determination of (Kushner), 1046  
 is time of, dependent upon histologic structure of membranes (Apajalahti), 363 (Abst.)  
 or high puncture of, induction of labor by (Smythe and Thompson), 364 (Abst.)  
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 as method of inducing labor (McCord), 587  
 spontaneous, effect on deliveries of (Fredrikson), 363 (Abst.)  
 of pelvic inflammatory masses into urinary bladder (Falk and Hochman), 654  
 of uterus, pregnant, from indirect injury (Stapleton), 368 (Abst.)  
 of vasa previa in twin pregnancy, velamentous insertion of cord with spontaneous (Kobak and Cohen), 1063
- Ruptured interstitial pregnancy after salpingo-oophorectomy on same side (Bartlett), 718
- S
- Sa Maternidade (Moraes), 542 (B. Rev.)
- Salpingectomy, interstitial pregnancy following (Forman), 344
- Salpingitis, tuberculous, tubal pregnancy with (Stein), 1068
- Salpingo-oophorectomy, ruptured interstitial pregnancy after, on same side (Bartlett), 718
- Salt balance and water exchange in hyperemesis gravidarum (McPhail), 305
- Scars, laparotomy, endometrioma of (Hewitt), 356
- Schwangerschaftsunterbrechung aus Urologischer Indikation (Ottow), 542 (B. Rev.)
- Secretion, gastric, effect of pregnancy on (Labate), 650
- Semen, fertile, criteria for (Brunner), 608 (Abst.)  
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- Serum estrogen in normal pregnancy (Rakoff), 373  
 in toxemias of late pregnancy (Rakoff), 375  
 of pregnant women, estrogenic and gonadotropic hormones in, studies on concentrations of (Rakoff), 371  
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 prolactin in normal pregnancy (Rakoff), 374  
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- Sex and internal secretions (Allen, Danforth, and Dolsy), 543 (B. Rev.)  
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- Sexually mature woman, biologic effects of testosterone propionate in (Salmon, Geist, and Walter), 264
- Sigmoidal cutaneous (fecal) fistula (Mendelsohn), 172
- Skull bones, overmolding of, causing fits in infant (Gordon), 181 (Abst.)
- fractures of newborn (Erbsloeh), 180 (Abst.)
- Smear, vaginal, human, evaluation of, in relationship to histology of vaginal mucosa (Geist and Salmon), 392
- Society transactions, Chicago Gynecological Society, 177, 362, 549, 735, 1082
- Brooklyn Gynecological Society, 1082
- New York Obstetrical Society, 362, 735
- Obstetrical Society of Philadelphia, 362, 549
- Pittsburgh Obstetrical and Gynecological Society, 735
- Sodium pregnandiol glucuronide, urinary titers of (Hamblen, Powell, and Cuyler), 563
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- Stain, vaginal, smear, technique of (Geist and Salmon), 393
- Stereocentrometry, pelvimetry by (Johnson), 361 (Abst.)
- Sterility and amenorrhea—surgical treatment of bilateral polycystic ovaries (Stein and Cohen), 465
- Sterilization, tubal, by Madlener technique (von Graff), 295
- Streptococcal infections, hemolytic, treatment of, during pregnancy and puerperium, with sulfanilamide and immunotransfusion (Chandler and Janeway), 187
- Streptococcus viridans endocarditis in pregnancy (Page and Campbell), 97
- Suburethral abscesses, urine pockets and diverticula in female urethra (Schmitz and Nelson), 707
- Sulfanilamide and immunotransfusion, treatment of hemolytic streptococcal infections during pregnancy and puerperium with (Chandler and Janeway), 187
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- use of (Morris), 67
- in treatment of gonorrhea in female (Grodberg and Carey), 533 (Abst.)
- passage of, through human placenta (Speert), 711 (Abst.)
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- intervention in obstetric practice (Meilroy), 368 (Abst.)
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- prenatal, a preventable disease (Zakon), 552 (Abst.)
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- of dysmenorrhea with (Salmon, Geist, and Walter), 264
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- internal cone and its role in ovulation (Strassman), 145 (Abst.)
- Therapy for placenta previa, best form of (Lipfelt), 1084 (Abst.)
- Thiobarbiturates in obstetrics: pentothal and thioethamyl (Bourne and Pauly), 692 (Abst.)
- Thrombocytopenic purpura cured by splenectomy, severe menorrhagia as only symptom of essential (Israel and Mendell), 339
- Thrombocytic colitis (Bargen, Nunez, and Mussey), 146
- Thymus shadow, relation between birth weight and size of, in newborn (Donaldson), 178 (Abst.)
- Toxemia mortality in Southern States (Bradford), 574
- obstetric management of patients with (Dieckmann and Brown), 214
- of pregnancy (Strauss), 199
- pre-eclamptic, concentration of serum sulfate during pregnancy and in (Hunt and Wakefield), 498
- pregnancy, anterior pituitary-like hormone in late (Smith and Smith), 618
- Toxin, circulating vascular in eclampsia (Page and Ogden), 233
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- placental blood for (Howkins and Brewer), 727 (Abst.)
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- vaginitis, treatment of, instrument for (Robinson), 1081

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- Uterine and placental circulations, changes in, during different stages of pregnancy (Kearns), 400  
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- Varicose veins of broad ligament (Salatic), 177 (Abst.)
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- Vascular lesions in decidua basalis (McKelvey), 815
- Vegetative changes, associated with menopause, nervousness due to (Young), 115
- Veins, varicose, of broad ligament (Salatic), 177 (Abst.)
- Velamentous insertion of cord with spontaneous rupture of vasa previa in twin pregnancy (Kohak and Cohen), 1063
- Version and extraction in delivery of overdeveloped fetuses (Koff and Potter), 416
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- Vesicovaginal fiber bundle of female pelvis (Power), 30
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- Vitamins in pregnancy (Dicckmann and Swanson), 527
- Vomiting of pregnancy, control of, relation of pregnancy to biliary disease and (McGowan and Baker), 555 (Abst.)
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Group A. Mechanically easy delivery of apparently normal infants, with death occurring a few hours to several days later, with evidences of intracranial hemorrhage.

Group B. Mechanically easy delivery, with stillbirth, or birth of a child in manifestly poor condition who cannot be revived or who dies shortly afterwards.

Group C. Mechanically difficult or traumatic delivery.

For the 8 deaths in Group A little need be said, except to comment again that this group constitutes the type of case in which the hazards of the mechanism of breech delivery per se are chiefly involved.

The cases in Group B deserve some detailed consideration.

1894. No. 4444. Sudden loss of fetal heart after admission, 2½ hours before normal breech delivery. Baby stillborn.

\*1898. No. 9287. Breech delivered normally to umbilicus. Cord found pulseless. Rapid extraction done. Baby stillborn.

1907. No. 15273. Second twin. Extracted. No complications. Baby badly asphyxiated. Died in one hour.

\*1908. No. 15695. Normal first stage. Breech allowed to descend. Delivery not interfered with. Expulsion rapid. Arms not extended. No difficulty with the aftercoming head. Baby stillborn.

1913. No. 20253. Second twin. Stillborn. No details supplied by record.

TABLE IV. MECHANICAL MORTALITY IN BREECH DELIVERY

	GROUP A	GROUP B	GROUP C	TOTAL
1888 to Mar. 1, 1921				
Deaths following normal or assisted delivery	2	5	0	7
Deaths following extraction after full dilatation	0	5	3	8
Deaths following extraction before full dilatation	0	0	1	1
Deaths following extraction after manual dilatation	0	0	2	2
	2	10	6	18
Mar. 1, 1921 to 1937				
Deaths following normal or assisted delivery	1	0	0	1
Deaths following extraction after full dilatation	5	3	2	10
Deaths following extraction before full dilatation	0	0	0	0
Deaths following extraction after manual dilatation	0	0	2	2
	6	3	4	13

\*1915. No. 21702. "At time of delivery patient was unruly, and pushed buttocks of fetus out of vulva before arrival of house-officer." Arms and head easily delivered. Baby stillborn.

\*1918. No. 25307. With breech on perineum delivery was effected with finger in groin. No difficulty. Baby rigid. Gapsed once. Could not be revived.

\*1919. No. 25821. Fully dilated over an hour. Fetal heart irregular. Both feet delivered. Arms delivered. Head delivered. No difficulty. Stillborn.

1920. No. 26867. Fetal heart disappeared twenty-two minutes before delivery. Loop of cord found compressed by left leg. Easy delivery. Baby stillborn.

\*\*1920. No. 26899. Entered hospital three days before delivery for ante-partum hemorrhage and ? of ablatio placentae. No hemorrhage after admission. Ruptured membranes twenty-four hours before onset of labor. Fetal heart irregular from start of labor. Voorhees' bag inserted, and came out in 2¼ hours. Os fully dilated. Easy extraction. Baby stillborn.

1930. No. 2402. Extraction at full dilatation. Easy delivery. Baby in poor shape at delivery. Died seven hours. No autopsy.

1931. No. 5400. Extraction at full dilatation. Gapsed on perineum. Did not breathe after delivery. Autopsy showed 50 c.c. of blood in subdural space, and a bilateral tentorial tear.

TABLE I. DELIVERIES OF BREECH PRESENTATIONS AT THE BOSTON LYING-IN HOSPITAL FROM 1888 THROUGH 1937

	DELIVERIES	WELL	STILLBORN OR DIED	MORTALITY
A. Breech deliveries (2035)				
1. Uncomplicated				
a. Primiparous (691)				
(1) Premature	102	45	57	55.8%
(2) Immature	89	77	12	13.4%
(3) Mature	500	449	51	10.2%
b. Multiparous (768)				
(1) Premature	119	54	65	54.6%
(2) Immature	89	85	4	4.5%
(3) Mature	560	514	46	8.2%
2. Complicated (453)				
3. "Nonviable" (123)				
(Macerated and mal-formed)				
B. Cesarean sections (58)				
1. Uncomplicated (52)				
a. Primiparous	32	31	1	3.1%
b. Multiparous	20	18	2	10.0%
2. Complicated (6)				

TABLE II. MORTALITY IN BREECH DELIVERY. MULTIPAROUS MATURE SINGLE INFANTS (1913-1937)

	DELIVERIES	WELL	STILLBORN AND DIED	INC.	MECH.	MORTALITY
1913 -1921(p)	88	75	13	6	7	14.5%
1921(p)-1927(p)	100	93	7	3	4	7.0%
1927(p)-1932(p)	100	96	4	0	4	4.0%
1932(p)-1937	100	95	5	1	4	5.0%

TABLE III. MORTALITY IN BREECH DELIVERY, MATURE INFANTS, BEFORE AND AFTER MARCH 1, 1921

	DEL.	WELL	STILLBORN AND DIED	INC.	MECH.	MORT.
Primiparous, single						
1888—Mar. 1, 1921	183	152	31	1	30	16.9%
Mar. 1, 1921—1937	299	280	19	3	16	6.3%
	482	432	50	4	46	10.4%
Primiparous, single and multiple						
1888—Mar. 1, 1921	196	164	32	1	31	16.3%
Mar. 1, 1921—1937	304	285	19	3	16	6.2%
	500	449	51	4	47	10.2%
Multiparous, single						
1888—Mar. 1, 1921	204	178	26	10	16	12.7%
Mar. 1, 1921—1937	300	284	16	4	12	5.3%
	504	462	42	14	28	8.3%
Multiparous, single and multiple						
1888—Mar. 1, 1921	231	202	29	11	18	12.5%
Mar. 1, 1921—1937	329	312	17	4	13	5.1%
	560	514	46	15	31	8.2%

The role of abdominal cesarean section for delivery of breech infants in multiparous women is decided upon grounds which differ in some degree from those which make this operation advisable in primiparas. In the latter type of case the real question is ordinarily that of fetopelvic, especially of cephalopelvic, disproportion, a decision which may require both clinical and x-ray measurements for its determination ante partum. In the former, however, a more or less accurate guide is presented by the history of the previous labor or labors. Antecedent delivery of one or more healthy full-term infants through the pelvis gives presumptive evidence of the adequacy of the maternal structure for delivery of her present infant by the same route; on the other hand if the previous labors have resulted in stillborn or traumatized children, the presumptive evidence favors the use of the abdominal route, and both clinical measurements of the pelvis and x-ray measurements of the fetus assume urgent importance.

The 20 abdominal sections upon multiparas at full term are summarized in Table VI, separating them into those done before 1932 and those performed thereafter with benefit, potential or actual, of x-ray mensuration. In the first group of 13, 7, or over half, were done because of previous obstetric catastrophes; 4 had had previous sections; 1 was done for "small conjugate" in a patient with one child living and another stillborn following craniotomy upon a hydrocephalic infant in breech presentation, and 1 was done in a patient forty-four years of age in the presence of hemorrhage in the first stage of labor. Of the 7 cesarean sections done in 1932 and subsequently, 6 were done because of a previous section and 1 in the presence of an obstructing dermoid cyst. It is of interest to note that x-rays were used for fetal measurements in only 2 of these 7 cases, as contrasted with the employment of roentgenometry in 12 of 19 primiparous breech cesarean sections during the same period. Two of the 20 infants obtained by section in the entire series died: one of hydrocephalus, and another on the eleventh day of erysipelas.

TABLE VI. INDICATIONS FOR CESAREAN SECTION IN MULTIPAROUS BREECH DELIVERY

	NO. CASES	X-RAYS
<i>1899* through 1931</i>		
A. One or more previous stillbirths or early neonatal deaths following previous difficult pelvic deliveries	7	0
B. One or more previous cesarean sections	4	0
C. Contracted pelvis ("small conjugate") plus previous craniotomy for breech and hydrocephalus	1	0
D. Ante-partum first stage bleeding in woman of 44	1	0
<i>1932 through 1937</i>		
A. One or more previous cesarean sections	6	1
B. Dermoid cyst in pelvis blocking labor	1	1

\*First cesarean section recorded for multiparous breech presentation was in 1899.

In this small series the conclusions are evident that fetopelvic disproportion in the multiparous breech presentation at term may often be predicated either upon the history of previous obstetric catastrophes, or upon the previous necessity for abdominal section. At the same time the advisability of routine x-ray investigation is evident not only when any suspicion of disproportion may exist—as in the case where the baby seems overlarge—but also to avoid the distressing accident of performing a cesarean upon a patient whose infant is grossly malformed.

1937. No. 17698. Fetal heart disappeared twenty-one minutes before delivery. Easy extraction. Cord around neck and arm. Baby stillborn. Autopsy showed intrauterine asphyxia but no other trauma.

It is evident that 8 of these 13 cases occurred among the 231 deliveries previous to March 1, 1921, e.g., in the era of conservatism, while only 3 occurred among the 329 deliveries subsequent to the adoption of the activist policy. It seems to me, at least, that the 5 fatalities illustrated above marked with an asterisk might not have occurred had earlier extraction been instituted, whereas an early resort to abdominal delivery might have saved the case in 1920 designated with a double asterisk.

The 10 fatal cases in Group C, where delivery was frankly difficult, are summarized as follows:

In 3 instances infants weighing between 6 and 7 pounds were delivered through contracted pelvis. Their deaths must be laid to misjudgment of fetopelvic relationships, although in one case the delivery was effected through an incompletely dilated cervix.

In 4 instances delivery was effected following manual dilatation of incompletely prepared cervixes.

In 3 instances large infants, weighing over 9 pounds, were delivered following full dilatation. In all cases difficulty was remarked upon, and though in one the note is made, "baby not injured in extraction," in the other two autopsy showed respectively vertebral and intracranial damage. The suspicion is evident that these three deaths may have been due to fetopelvic disproportion resulting from the large size of the infants.

In this study, as was the case in the primiparous series, the results of normal or assisted delivery between 1888 and 1912 might seem to indicate that conservatism was the method of choice. Table V shows that this policy resulted in only 9 stillbirths and neonatal deaths among 101 infants born, of which only 4 were definitely based on mechanical causes. Extraction, on the other hand, resulted in 6 such deaths among 35 infants born. It must be recalled, however, that during this era extraction was customary only in cases in which normal delivery had "failed" for one reason or another, and that the really difficult cases were all grouped under this method of management.

In brief recapitulation it should be said that experience with multiparous breech delivery at the Boston Lying-in Hospital over a period of fifty years shows mortality rates closely similar to those obtained in primiparas; in both groups the study of mortality rates and analysis of stillbirths and neonatal deaths which have occurred give strong support to the conclusion that routine extraction of the infant under full surgical anesthesia after full dilatation of the os in relation to the breech has been attained is safer for the infant than the policy of normal or assisted delivery.

TABLE V. COMPARISON OF MORTALITY FOLLOWING BREECH "DELIVERY" AND BREECH "EXTRACTION"

(1888-1912)

	TOTAL CASES	DEATHS	INC.	MECH.			MORT.
				GROUP A	GROUP B	GROUP C	
Normal or "as- sisted" delivery	101	9	5	1	3	0	8.9%
Extraction	35	6	0	0	1	5	17.1%

The relegation of nervousness to the cessation of menstruation certainly deserves careful appraisal. In this paper, the attempt will be made to discuss first, the menopause from the standpoint of the associated changes as they affect the body and the individual; second, the nervous symptomatology that occurs at the time of the menopause; third, diagnostic points that deserve consideration; and last, plans for treatment.

### MENOPAUSE

The menopause refers to the cessation of menstruation, but this manifestation is only one sign of the involutional changes that take place. From a physiologic standpoint, the cessation in follicular activity is accompanied by changes in other endocrine organs, as well. Usually the estrin content of the blood is decreased, and there is a marked increase in gonadotropic hormone, indicating an acceleration in anterior pituitary activity. Also, both hyperthyroidism and hypothyroidism occur at this time. Virilism, increased facial hair, a change in voice, atrophy of the genital tract, and obesity are associated conditions.

Besides the above-mentioned physiologic manifestations of the menopause, there are certain personality readjustments that must take place. Much has been written about the personality adjustment that comes with puberty and adolescence, but there is very little that deals with the menopause. In particular, the psychologic implications of the menopause have been neglected. If one goes back to early mythology or explores the folklore of the different cultures, women are linked with mystical powers by virtue of menstruation. Havelock Ellis has remarked that everywhere menstruating women were supposed to be possessed by spirits and charged with mysterious forces. The cessation of the menstrual flow implies a castration experience, in the sense that the woman no longer has the ability to bear children. The loss of this power, plus the loss of certain other less well-formulated forces associated with menstruation, has a definite effect upon the sexual adjustment. In an unmarried woman, the loss may be more keenly felt as a potential force that has never been utilized, being gone forever. In the last analysis, the goal towards which the libidinous feelings are directed is family formation, and any experience that influences child-bearing calls for modification of the sexual life of the woman.

With the menopause, there is usually a slow decline in the sexual pace. Frequently, this is ushered in by a temporary increase in sexual drive that precedes the menopausal changes. This increase in libido may present a difficult problem to the woman in sexual adjustment, particularly if the needs are not recognized by the husband.

Other personality changes, as irritability, apprehensiveness and aggressiveness, have been described. In some women there appears to be a definite decrease in interests or an apparent lack of driving force.

Besides the personality changes due directly to the menopause, there are certain other factors that appear at this life period which are not connected with the menopausal changes. Most women at about the age of 45 to 50 experience a change in the family life. Children, who for

## CONCLUSIONS

1. The cases discussed in this survey have been limited to normal multiparas at or near term with infants in utero, all weighing 6 pounds or over.

2. The management of breech delivery in the multipara by abdominal cesarean section is especially to be considered in cases where previous delivery has resulted fatally for the infant, and in cases in which previous delivery has been accomplished by cesarean. Both of these obstetrically antecedent events suggest fetopelvic disproportion.

3. In selected cases, where the pelvis is clinically contracted or when the infant is deemed overlarge, x-ray measurements may suggest abdominal delivery even though the patient has previously borne one or more normal children.

4. In any case in which abdominal delivery is contemplated, it is a wise policy to use the x-ray, not only to confirm and control the size of the infant but also to detect gross skeletal abnormalities undiscovered by clinical examination.

5. If pelvic delivery is selected, the second stage of labor should be terminated by breech extraction under full anesthesia before the birth of the umbilicus, as classically recommended, has occurred.

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475 COMMONWEALTH AVENUE

## THE RELATIONSHIP OF NERVOUS DISORDERS TO THE MENOPAUSE\*

RICHARD H. YOUNG, M.D., OMAHA, NEB.

SINCE the time of Araeteus, there has been a trend to interpret nervousness in women as a dysfunctioning of the generative organs of the body. Two thousand years ago, it was acceptable to look upon an anxiety state, with its suffocation symptoms, as due to the upward wandering of the uterus exerting pressure upon the diaphragm. However, today, behavior, even though it be nervous behavior, deserves a more comprehensive analysis than the reduction of the problem to the functioning of an organ or set of organs in the body. Human behavior is the functioning of the individual as a whole, and can never be understood or its disorders treated in terms of one part of the body.

In spite of the many factors involved in the production of nervousness in women, this common complaint is often linked with menstrual or menopausal manifestations. Too frequently, nervousness in women between the ages of thirty and forty is glibly reduced to a "premature menopause." Where the age range is between forty and fifty-five, the "menopause" offers a handy explanation, and nervousness after the age of fifty-five may be attributed to "getting over the menopause."

\*Read at a meeting of the Omaha Mid-West Clinical Society, October 25, 1938.



they developed, their course and the patient's adjustments to events in the past. In evaluating the minor or neurotic symptoms of the menopause, the prime query should be whether or not the patient has experienced neurotic symptoms in the past. Almost invariably, patients do not develop a neurosis for the first time in their lives after the age of forty-five. If a woman is able to go through forty-five years of her life without neurotic symptoms, she will not subsequently develop a neurosis on a psychogenic basis. Using this simple diagnostic rule, it may be said that women with a negative neurotic history who complain of minor nervous symptoms at the menopause have a symptomatology related to the associated physiologic menopausal changes. Women in this class constitute a relatively small group.

The majority of women with minor types of nervousness are patients who have been psychoneurotics for years, and have experienced an exacerbation of symptoms with the climacterium. Frank<sup>2</sup> and his associates state that the more nervous and more maladjusted before the menopause, the more severe the symptoms.

The major types of nervous reactions may be distinguished by their more sweeping nature, their involvement of the whole personality. This is shown by the loss of sleep and weight, and mood change and content of thought. The schizophreniac or dementia precox type of reaction can be distinguished by the oddities and incongruities in behavior that usually carry back to early adult life. The paranoid developments can be detected by the nature of the false beliefs.

Organic psychoses may simulate in early stages the minor type of menopausal nervousness. In such cases, there is usually the history of a good past performance, with freedom from neurotic traits. With the onset of nervousness and behavior change in a woman of 45 to 55 with a negative past history, an organic psychosis, due to brain disease, and particularly paresis, should be suspected. The presence of an intellectual deficit and positive spinal fluid confirms such a diagnosis. The frequency with which women in this age group, suffering from paresis, have had their nervous symptoms related to the menopause, has been commented upon by Campbell.<sup>3</sup>

The depressive psychoses are diagnosed by the evidence of sadness, retardation of activity, self-condemnatory thinking, loss of sleep and weight, plus the other symptoms mentioned in the section on symptomatology. The diagnosis of involutional melancholia is usually made, chiefly because the women are in the involutional period. However, involutional melancholia constitutes a very small nosologic group, and consists of those depressed reactions which are characterized by agitation, a harping hypochondriasis, and well-rutted patterns of depressive thinking. There is no more reason to class as involutional all depressions at this period than there is the anxiety states, hypertension, or any other disease that occurs at the menopause. Many of the depressions occurring at the time of the climacterium are almost exactly the same in symptomatology, even to the content of delusional beliefs, as the depressions experienced earlier in life.

years have been dependent and who have absorbed a great share of interest and affection, emancipate themselves from the family and find new love objects. The result is that the woman again experiences a lack of satisfaction, which, without plasticity of the personality and an ability to find new interests, may make for difficulties in personal adjustment. Other stress or strain, such as the loss of a husband, or financial reverses, is harder to meet at this time of life because the opportunity for re-establishment of security wanes with the years.

#### SYMPTOMATOLOGY

The nervous symptoms that appear at the time of the menopause are of two main types, those that are minor and directly related to the menopausal changes, and the other larger group, whose relationship to the menopause is merely temporal.

The nervous symptoms most commonly related to the menopause are those of essentially vegetative origin, and include hot flushes, sweating spells, feelings of internal nervousness and palpitation. Associated with these sensations are feelings of tenseness that express themselves in the emotional life of the individual, as apprehensiveness, irritability, swings in mood, an easy tearfulness, and an inability to meet stress and strain. In addition to these minor symptoms, the psychosis, involutional melancholia, has been classed as a menopausal disorder by Werner and his associates.<sup>1</sup> This relationship is questioned and will be discussed later.

Other nervous symptoms occur at the time of the menopause, but as has been stated, it is probable that the relationship is only temporal.

Nervous symptoms may be classed into two groups, the minor or psychoneurotic, and the major or psychotic type.

The psychoneurotic symptoms are chiefly those of a tension and anxiety type, with panicky outbursts and attending somatic symptoms, such as drawing pains in the back of the neck, tight feelings in the throat, suffocation sensations in the chest, and pounding of the heart, chiefly symptoms above the diaphragm.

The psychotic symptoms involve the individual in a more sweeping, widespread manner, causing loss of sleep, appetite, and weight. The symptomatology varies with the class of psychosis. Probably most prevalent are the depressive reactions, with intense feelings of sadness and hopelessness, suicidal preoccupations, and ideas of a self-condemnatory and self-depreciatory type. Another psychotic reaction is the paranoid development, which so frequently centers about the delusion of the husband's infidelity. Less frequent are false beliefs about the oppressive activity of neighbors. At times, psychotic symptoms of an unrelated organic psychosis may appear at this period, with a symptomatology that includes irritability, errors in judgment, memory deficits and widespread changes in the personality makeup.

#### DIAGNOSIS

Of utmost importance in psychiatric diagnosis is a careful consideration of the patient's verbatim complaints, the conditions under which

3. *Depressive Psychoses.*—The patient with a depressive psychosis that occurs at the time of the menopause should first of all be hospitalized. A depressed patient is unable to meet the ordinary life situations, and becomes increasingly more depressed and frequently commits suicide. Werner and his associates<sup>1</sup> have presented a strong claim for the treatment of depressions during the involutional period with theelin. However, this work has not been confirmed.

In our practice, the prognosis of the depressive reactions has been improved and the period of hospitalization immeasurably shortened by the use of the metrazol treatment, which was first utilized in cases of the schizophrenic psychosis. Dr. G. A. Young and I reported our results with metrazol in the depressions at the A. M. A. last June,<sup>7</sup> and subsequent experience has re-enforced our favorable impression of this type of treatment. We have treated 14 women with depressions, with an age range of from 40 to 60, with the complete recovery of 78 per cent, the improvement of 22 per cent, and failure with the treatment in none.

The convulsive treatment, while disturbing to the patients, shortens the course of treatment from months to weeks. The average treatment period is about three weeks. An additional short period is necessary for psychotherapeutic work and stabilization of the good feelings.

4. *Paranoid Developments.*—Treatment of such disorders is along psychiatric lines with the patient hospitalized. Insulin and metrazol have become valuable adjuncts to the older psychotherapeutic methods.

5. *Organic Psychoses.*—Again hospitalization is required with treatment depending upon the type of organic disease present.

#### COMMENT

In this article, an attempt has been made to draw attention to the menopausal period as one of importance in the life history of the individual. Changes occur at this time that have profound influence at both the physiologic and the higher psychic, or psychobiologic levels of functioning. The changes in functioning produce effects that influence the functioning of the parts and the functioning of the body as a whole. One of the symptoms of change is a type of symptomatology that can be classed as "nervousness." In the evaluation of this complaint, it is necessary to view the total complaint picture and to study thoroughly the situation in which it developed. Care must be taken to discover whether or not the nervous symptoms are of recent origin, long-standing in nature, or an exacerbation of former neurotic difficulties.

From a diagnostic standpoint, it must be decided whether nervousness is major or minor in type and how much of the symptomatology is due to the physiologic change of the menopause, and how much might be attributed to other factors, physical, situational and emotional.

Treatment must be along broad lines which take into consideration all the facts in any given case. Such a plan will include, when indicated, the use of drugs whose effect is chiefly upon the vegetative nervous system, administration of endocrine products, situational alteration, and work with the personality problems involved.

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## TREATMENT

Treatment must be based upon a proper diagnosis, and while it is impossible to classify the cases into diagnostic pigeon-holes, a broad classification will be attempted for the sake of formulating plans for therapy.

1. *Nervousness Due to the Vegetative Changes Associated with the Menopause.*—For some time now, there has been a wholesale use of the follicular hormone as the chief therapeutic agent in this group. The different pharmaceutical houses have assiduously circularized the medical profession with information and favorable reports of various authors. This is an attractive type of therapy because the use of any substance extracted from the gonads has a strong emotional appeal, an appeal because of implied rejuvenation effect and a veiled promise of postponement of the loss of sexual power. Several years ago there was editorial comment\* that physicians, not to be outdone by their colleagues, demand the hormones (from the manufacturers) as rapidly as they can be separated from the tissues, blood or excreta of animals or man, and proceed to inject them into patients.

There is reason for the use of estrogenic substance, in that the estrin titer is low during the menopause, and its injection causes a decrease in the excessive amount of gonadotropic substance. However, estrin injected is expensive, quickly excreted, and the beneficial results obtained are temporary. Where a trial is given, it is necessary to use 30,000 to 50,000 units weekly, and after an initial period of intramuscular injection with relief, smaller doses may be given and the substance administered orally. Several authors have raised the question as to the possible carcinogenic action of estrogenic substance, but this is at present merely a conjecture. Unfortunately, there is a paucity of reports on the poor and complicated results of treatment with the estrogenic substance.

Other considerations for treatment must include the use of small inhibitory doses of x-ray to the pituitary, in an effort to cut down the over-activity of the anterior pituitary hormones. This treatment is without danger, and is recommended by Collins, Thomas and Menville.<sup>5</sup> Cold effervescent drinks offer momentary relief for the hot flushes. Belladonna alone, or in combination with ergot derivatives, has been recommended for the vegetative manifestations; and Campbell<sup>3</sup> has used Lugol's solution in cases which appeared to have hyperthyroid manifestations. Sedatives for this type of nervous reaction are not recommended. An excellent statement from Ehrenfest's<sup>6</sup> review of the subject concludes with these remarks on treatment of this type of nervousness, "For the majority of worried, frightened and emotionally disturbed women, premenopausal or postmenopausal, a quiet, encouraging and occasionally reiterated explanation of the situation proves the most helpful and effective sedative."

2. *Psychoneurosis with Exacerbation at the Time of the Menopause.*—In this group are the largest number of women who complain of minor types of nervousness at the menopause. For these cases, the chief therapeutic attack must be made along psychotherapeutic lines. Simple measures, such as a careful consideration of the complaints and history, a thorough examination, a complete explanation of the nature of the disorder, reassurance, a discussion of the personal, emotional and situational factors of stress and strain, with help in planning for a more satisfying existence, accomplish results with these patients that far exceed those obtained with medication. Sedative tub baths for half an hour twice a day, and massage, are better than sedative medication. Estrogenic substance is only a secondary or supplementary type of treatment, and at that, of doubtful benefit.

The anxious patient needs repeated reassurance and frank discussion of the emotional problems, frequently in the psychosexual field, that are producing the tension. In the anxious and tense woman, every effort must be made to re-establish security and to find satisfying activities and interests toward which her driving forces and energies may be directed.

Students of this disease have been much interested in its clinical aspects in an effort to find the best way to explain recurrent acute exacerbations and some have gone so far as to say that pyelitis in childhood is important in this respect. Our study does not add impressive weight to this point of view as only 12, or 10 per cent, gave a past history of pyelitis. Three of these had had a previous attack of pyelitis in this hospital during the time of study. Four only were primigravidas and gave a history of pyelitis in childhood or prior to the onset of a pregnancy. In the post-partum group, 5 had had a previous history of pyelitis, one in a former pregnancy, and the other 4 prior to the onset of their first pregnancy.

So little has been done to correlate pyelitis in infancy and childhood with pyelitis in pregnancy that it is practically impossible to recognize earlier infection as a factor in later attacks. A small group of children with pyelitis has been followed by Wharton, Gray and Guild, and their results are published in the *Journal of the American Medical Association* (109: 1597, 1937). Their report reveals that 57 per cent of these children had abnormal urinary tract findings in adult life, only two became pregnant, and one of these developed pyelitis. However, the series is too small to draw any conclusions as to the effect of childhood pyelitis upon the kidneys during pregnancy.

DeLee emphasizes the increased incidence of pyelitis in patients suffering from toxemia while Bear and others have noticed a decreased occurrence. The incidence of toxemia in our clinic population is about 10 per cent which corresponds almost exactly with that of toxemia associated with ante-partum pyelitis. On the other hand, in the puerperium, 24 per cent of the patients who developed pyelitis had developed a toxemia of pregnancy during the ante-partum course. This great increase in the latter percentage as contrasted with the ante-partum group is at first quite startling, but on closer study of the 15 patients with toxemia who developed post-partum pyelitis, it was established that in 7 of them the attack of pyelitis immediately followed the kidney function test performed after delivery. In explanation it should be stated that in this clinic, the urea clearance test and fractional phenolsulphonephthalein test are done on the same day in the post-partum period, necessitating the use of an indwelling catheter for a period of from four to five hours. The microscopic study of the urine at the time of the first test was negative, but several days later when the second test was performed the microscopic urine usually contained a definite number of white blood cells and within two or three days of the second test, pyelitis developed. While not conclusive, we feel that this is very suggestive evidence that 7 of these 15 patients were infected at the time of the kidney function test, and if these 7 are eliminated the incidence of toxemia among the post-partum pyelitis group falls to about the incidence of toxemia for the whole clinic. Our study, therefore, fails to substantiate the point of view of those who feel that there is an intimate relationship between toxemia of pregnancy and pyelitis.

Of the 98 ante-partum patients, 20 were not sufficiently worked up or refused to return for investigation, and consequently cannot be used

# PYELITIS OF PREGNANCY

## A FIVE-YEAR STUDY

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FROM the time of the opening of this Clinic in September, 1932, we have been impressed by the number of patients who developed pyelitis in their pregnancy, for there seemed to be many more than we had formerly been led to believe from the reports of other clinics. During this time we have conducted a thorough study into etiologic factors causing pyelitis as well as the clinical aspects of the disease; most of the details of our work have been previously reported and are available in the literature. However, as there is a dearth of information with regard to the sequelae of pyelitis it seems wise that we should report our later findings in patients studied. The only sizable report of this nature in the English language came from the Boston Lying-in Hospital a number of years ago, and much of its information was based on older methods of study. We wish, therefore, to add somewhat to the knowledge of this aspect of the problem by reporting what our results have been from September, 1932, to September, 1937.

During this time there occurred 168 cases of proved pyelitis in a total of 14,000 deliveries. Many more than this number of case histories were studied but all others were discarded because of insufficient evidence of definite pyelitis. This gives us an incidence of 1.2 per cent for pyelitis of pregnancy, whether ante partum, intra partum or post partum. These 168 cases occurred in 164 patients as 4 patients had two attacks during this period of study.

This residual group of 168 was subdivided into those who developed their pyelitis during the ante-partum period with or without a subsequent post-partum flare-up, those who developed a pyelitis during labor, and those who developed it during the post-partum period. There were 98 cases of ante-partum, 62 cases of post-partum, and 8 incidences of intra-partum pyelitis. Because the latter group is so small, it has been included in the ante-partum group in coming to most of our conclusions.

We do not wish in this paper to obscure conclusions by a multiplicity of statistics but in such a study, a certain number of them is necessary, and we shall take these up as briefly as possible, discussing them fully whenever plausible.

It is commonly stated that pyelitis is more common in primigravidas than in multigravidas. In this series there seems to be no particular predilection in either group, for of the 98 ante-partum patients, 46 were primigravidas and 52 multigravidas, in the 62 post-partum patients, 34 were primigravidas and 28 multigravidas, and in the 8 intra-partum patients, 2 were primigravidas and 6 multigravidas.

nection between the pyelitis and the unfortunate outcome in these latter two pregnancies, because the acute pyelitis in both patients cleared up early in pregnancy, and there was no subsequent attack. However, both did continue to have positive cultures through their ante-partum courses.

In this same group of 10 patients the cultures in 2 who were allowed to go to term became negative during pregnancy; 2 others became negative within three months of the time of delivery or interruption; 3 became negative at from three to six months, and 3 became negative under twelve months. We think that it is fairly unusual for all these patients to have had negative cultures in less than twelve months, because in the remaining 88 ante-partum patients, 14 had positive cultures for longer than a year. It is possible that if the disease develops early, is recognized and treated radically, the prognosis for the patient is better from the point of view of positive or negative urine cultures.

In the whole group we attempted to correlate the time of onset of pyelitis with the duration of the fever in the acute attack and with the type of treatment in an effort to see whether the date on which the ureteral cultures became negative might depend on the time of onset or type of treatment. We divided our treatment into three groups—treatment by conservative methods only, conservative treatment plus cystoscopy, and a combination of these two forms of therapy with mandelic acid. Unfortunately in the 98 patients, only one was treated with complete conservatism, and only 7 combined all three forms. These eight are not enough from which to draw any conclusions but in the 90 patients who were treated by a combination of conservative and cystoscopic methods, there did not seem to be any correlation between the onset, type of treatment, and time the culture became negative. Of the entire 98 patients, 46 had a febrile course post partum. Yet many of these had had an afebrile interval between the acute ante-partum attack and delivery. This interval was in some cases a matter of months. Evidence would tend to show that in the presence of positive cultures but in the absence of fever, the disease is in a chronic state and is capable of producing progressive fibrosis of the ureter and kidney pelvis. A post-partum flare-up is a natural result in a large percentage of these cases but can be avoided often by periodic dilatation of the ureters following the acute attack and before delivery.

Of the 38 patients who developed pyelitis in the first two trimesters of pregnancy and were cured of their acute attack long before the onset of labor, 22 had a febrile puerperium, 11 were afebrile, 4 were delivered elsewhere, and one died. When last seen during this period of study 24 of the group of 98 ante-partum patients had positive cultures.

The fetal mortality (including both the babies born at term who died, the prematures who died, and the abortions which had to be done because of the disease or which were caused directly by the disease) in the ante-partum group of 106 patients, was 15.8 per cent. There were 4 premature or full-term babies who failed to survive whose death was directly attributable to pyelitis, and there were 13 abortions as the result of pyelitis. The abortions, of course, were performed in an effort to

in the detailed part of the study. Of the remaining 78, 33 patients had a subsequent pregnancy in this hospital and four of these subsequently pregnant patients had a recurrence of their pyelitis, 8 had positive cultures from the ureters but no recurrence, 21 had negative cultures. Of the 62 patients who developed pyelitis post partum, 4 had subsequent pregnancies, and of these 4, one had a recurrence in a post-partum period subsequent to pregnancy, and 3 had negative cultures and no recurrence.

The incidence of a subsequent attack in the patients adequately treated is small, 5 in 168 cases. We cannot emphasize too strongly the importance of regular follow-up on patients who have had pyelitis until 3 cultures at monthly intervals are found to be negative. Most of our patients were treated by conservative methods and by cystoscopy though mandelic acid was used in a small group, and in the last year, sulfanilamide. The results of these two methods of treatment will be reported later when the series are sufficiently large.

A subsequent pregnancy was discouraged until the cultures were negative for two years, and most of the patients received contraceptive advice, but needless to say many became pregnant sooner than we had hoped. It is interesting therefore to contrast those patients who were cooperative with those who failed to follow our advice, for in doing so it may be possible to gain some concept of the relationship between chronic infection and reinfection. In the case of patients who had had a severe first attack in pregnancy with residual damage, we feel that more recurrences were avoided by treatment between pregnancies and during subsequent pregnancies, even though their cultures were negative. Eight patients with positive cultures and many with negative cultures were followed through a second pregnancy by periodic cystoscopy and had no recurrence. The evidence seems to indicate that while it is desirable to obtain bacillus-free urine between pregnancies it is possible with diligent ante-partum care to guide patients having bacilluria through a subsequent pregnancy without having a flare-up of the disease. This possibility should not dull our desire to accomplish eradication of the infection because we have ample evidence to show that low grade chronic fibrosis is probably progressive in these patients as long as the infection persists.

Other studies have shown that pyelitis is essentially a disease of the third trimester of pregnancy and this is corroborated by our findings. Of the 98 patients, 60 developed pyelitis in the third trimester, 35 in the second and only 3 in the first.

It has been shown that when pyelitis develops before the sixteenth week of pregnancy, the prognosis for the patient is quite different from that which obtains when it occurs in the latter part of pregnancy. Treatment in these cases depends upon the persistence of the acute signs of the disease, the actual amount of kidney and ureteral damage and the response of the patient to therapy. Of the 10 patients developing pyelitis before the sixteenth week, 3 were necessarily treated by operative abortion and 6 were allowed to go to term. Of the latter group 4 delivered living babies and 2 dead babies. We can see no definite con-



of pyelitis or complications in which pyelitis was a contributing factor. There was an incidence of 3.58 per cent as compared to the mortality for the clinic during this five-year period of 2.4 per thousand pregnancies or 0.24 per cent. In other words the maternal chances of death are increased 16 times by an attack of pyelitis.

The physiology of the ureter in normal pregnancy has been the subject of extended study in this clinic and has been reported in *Surgery, Gynecology and Obstetrics*. To summarize very briefly, it was found that the ureter which had normal peristalsis and tone until the fourth month began to lose these functions gradually and by the sixth month the peristalsis and tone had practically disappeared. They returned again in the last month of pregnancy, were lost post partum, and finally became normal again about the time of the six-weeks' visit. The loss and recovery of function followed very closely the dilatation of the ureter and its return to normal size.

Parallel to this investigation of normally pregnant patients, many tracings on patients in various stages of pyelitis of pregnancy were also made. Several interesting facts concerning the function of the ureter in the presence of an infection were brought out in this way.

In the early acute phases of the disease, there is a definite increase in peristalsis and tone. We noted this same reaction in a nonpregnant patient with negative cultures but with a definite stricture of the lower end of the ureter. Absence of peristalsis and tone was generally observed in the last stages of the acute attack and persisted as long as the cultures remained positive. There seemed to be no definite relationship between dilatation of the ureter and lack of peristalsis in the infected patient. On the other hand, patients who had suffered pyelitis in a previous pregnancy showed no constant amount of peristalsis or tone in a subsequent pregnancy, regardless of whether the cultures were positive or negative.

It would, therefore, seem that tracings of ureteral activity might be the best indication of the extent of ureteral damage, since these are a direct graphic record of the contractility of the muscle fibers of the ureter and kidney pelvis. We frequently observed a lack of peristalsis and tone in one patient who had had a previous pyelitis while another would have normal function, the cultures in both cases being negative and the clinical course during the previous attack being more or less identical. This can be explained only by assuming that one patient had a greater degree of fibrosis in the ureter than the other and consequently poorer peristaltic function. A patient with fibrosis of the ureter and the associated inflammatory strictures has a greater chance for reinfection in a subsequent pregnancy, yet it is difficult to determine this condition by any of the other clinical methods.

#### CONCLUSIONS

1. Pyelitis in pregnancy is dangerous in two respects: (a) Maternal mortality of 3.58 per cent, and fetal mortality of 15.8 per cent; (b) exacerbations occur unless adequately treated or unless urine becomes bacilli-free between pregnancies.

preserve the health of the mother, but when we are attempting to determine the effect of pyelitis on pregnancy, they certainly must be counted as lost pregnancies for this group of patients.

As stated above, three of the abortions were done on or before the sixteenth week of pregnancy, and the remaining abortions or miscarriages were scattered between the eighteenth and the twenty-seventh week of pregnancy. It would seem that the babies of mothers suffering from pyelitis are unusually small because abortions or miscarriages performed as late as the twenty-fourth to twenty-seventh week yielded fetuses weighing only 500 to 750 gm.

There were 9 premature deliveries because of pyelitis, and of these, 3 babies failed to survive. When we add the 13 abortions and 9 prematures, we arrive at a figure of 22 failures to conceive viable offsprings in a total of 106 pregnancies, which result can be blamed directly on pyelitis. This is an effective commentary upon the results of pyelitis upon the child.

The onset of post-partum pyelitis in patients previously free of the disease occurred most frequently in the first week: 36 of 62 patients developed pyelitis at this time, 22 of these on the first day. The 7 patients whose pyelitis followed kidney function tests are not included in this group. The infection is almost always evident before the twenty-first day post partum; we had only 3 cases whose onset occurred after this time.

The explanation of the onset of pyelitis in the first week in over half of our cases is simple if one accepts the theory of lymphatic extension of the colon bacillus. It appears that in most instances pyelitis is secondary to a pre-existing infection of the lower genitourinary tract. We are of the opinion that the infection is carried from the bladder up the lymphatics of the ureter and paranreteral tissue to the kidney pelvis, and do not believe that the infection ascends the lumen of the ureter against the current of urine. In a previous study we have shown that immediately post partum, there is a relaxation and atony of the musculature of the ureters, giving a coincidental dilatation of the lymphatics which, in the presence of infection in the bladder and a lack of resistance on the part of the patient, can easily carry the colon bacillus to the kidney pelvis where it finds a ready medium for growth in the stagnant or slowly moving urine.

Additional proof of this theory of bladder infection can be given by stating that the duration of labor in our post-partum pyelitis group was about twenty-two hours as contrasted to the average duration of fourteen hours in a large group of normal multiparas and primiparas. In the 22 patients who developed pyelitis on the first day post partum, the average length of labor was twenty-two hours which means that for this period of time the bladder and lower urinary tract suffered constant impingement between the fetal head and more rigid structures of the pelvis. The high incidence of bladder infections following long labors is so well recognized as not to need further emphasis.

Reference has been made to fetal mortality. We must complete the picture by indicating the incidence of death in the mother, as a result

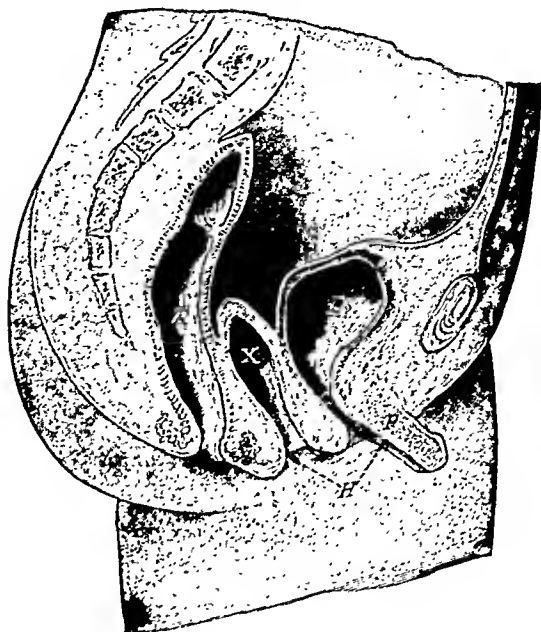


Fig. 1.—Diagrammatic representation of conditions in male pseudohermaphroditism of the hypospadiac type. Anteroposterior section showing the small hypospadiac penis with the urethra opening at its base and the enlarged sinus pocularis opening into the perineal vestibule. (From Crossen and Crossen, *Diseases of Women*, The C. V. Mosby Company.)

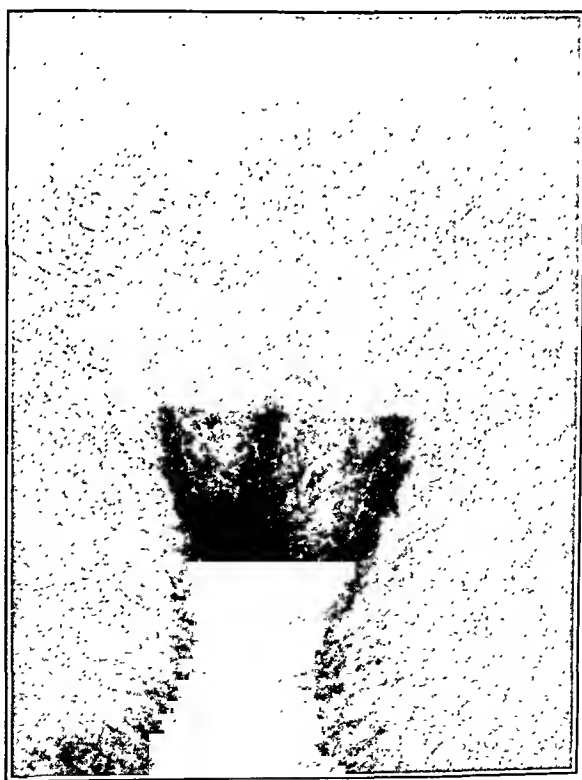


Fig. 2.—Showing the marked hair growth, with masculine distribution. The left testicle is coming down into the labium, while the right is higher in the groin.

2. Catheterization of the atonic post-partum bladder often leads to serious sequelae.

3. There is no proved relationship between toxemia and pyelitis of pregnancy.

4. The length of time during which the urine remains infected in the puerperium varies tremendously both in adequately treated and in untreated patients so that no definite conclusions can be drawn. Each patient is therefore to be treated individually.

5. As a result of acute pyelitis the patient sustains permanent ureteral damage due to fibrosis with embarrassment of peristalsis and ureteral tone.

For help in the presentation of this paper, I wish to express my appreciation to Dr. Herbert F. Traut, my collaborator in other studies on this subject.

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## A PROBLEM IN SEX CLASSIFICATION\*

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**M**ALFORMATIONS of the genital organs seldom impose any serious obstacle to the fundamental sex classification of the individual. In some cases abdominal operation is necessary to give definite information concerning the internal organs, but this usually clears the matter promptly. Even in the cases of mixed sex gland, that is, where one individual carries both ovarian tissue and testicular tissue, the sex determination is not difficult. All that is required is to preserve the gland tissue corresponding to the patient's preferences and instincts, and remove the other type. Occasionally, however, a case is encountered which is not covered by our usual methods of sex recognition and requires a much deeper consideration of what constitutes the real sex of an individual and how this primary sex may be modified or partly obscured by later pathologic developments. Such was the problem presented by the following recent case:

About the first of September, 1938, a young woman was sent to me for construction of a vagina. She was 28 years of age, and had never menstruated, though there had been some irregular bleeding when she was about 20 and again two years ago. On examination, I found the genital organs identical with those of a male pseudo-hermaphrodite. The conditions are shown diagrammatically in Fig. 1. There was the small hypospadiac penis, and back of that a vestibule with two openings, the one in front being the urethra, and the one a little farther back, an enlarged sinus pularis. The testicles were in the groins.

The general build was masculine, with narrow hips compared to the shoulders. As shown in Fig. 2 there is marked hair growth, with masculine distribution. Also, the patient had a beard requiring regular shaving. Fig. 3 gives a general view of the external genitals. The patient had more breast tissue than is ordinarily found in the male.

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\*Presented at a meeting of the Wednesday Conference of the Department of Obstetrics and Gynecology, November 2, 1938.

was the important and difficult problem which had to be worked out before anything could be done in the way of constructive surgery for the patient, because the type of surgical help required depended on whether the individual was to live as a man or as a woman.

If I followed the gonads and classified the patient as a male, I was directly opposed by the whole record of the individual's instincts, sexual desires and response, and the outlook into the future. If I followed the latter and classified the patient as a female, there was no ovarian tissue on which to rest the decision. A female with testicles and no ovary seemed paradoxical, and of doubtful authenticity. Still the patient had to be classified one way or the other. There was no neutral ground.

What are the dependable criteria for determining the primary sex of an individual? Of course, in this endocrine age, the gonads and their hormones occupy the center of the stage and are looked upon as the decisive factors in the sexual field. But are they? Such a case as this casts serious doubt on their fundamental importance in determining the primary sex personality. The gonad with its hormones may be an effect instead of a cause, as far as primary sex is concerned. Their influences are easily seen and may seem all-important, but there are other influences which enter into the building up of the instincts and directing forces. There is the whole nervous and mental system, which is as important a part of the individual as the gonads, and probably comes from just as strong genetic factors.

Wolf,<sup>1</sup> of the University of Bern, holds that in the chromosomal arrangement and determination of primary sex an impress is made on the somatic cells which takes precedence over that on the gonadal elements, which develop later. In discussing such cases, he states that the somatic and psychic impress seems predominant and that, though hormones play a role in later structural developments, the sex of the somatic cells is decisive. Novak,<sup>2</sup> in discussing his case mentioned later, states "such patients as I have described represent genetic females, in which gonadal reversal took place at a very early phase of development, with complete replacement of ovarian by testicular elements."

Reviewing then the two sets of phenomena which help in primary sex classification, we have in this case a personality with well-developed female instincts, preferences, sexual desires, and mental outlook, and on the other hand rudimentary male gonads and associated secondary developments. The testicles undoubtedly lack spermatozoa formation, and hence have stopped short of full development. The spermatic cords and prostate are still more rudimentary, being hardly appreciable in the abdominal exploration. The phallus is rudimentary, and resembles an hypertrophied clitoris as much as a hypospadiac penis. The canal in the perineum, which admits a finger for about an inch, may as well be considered a small vagina as an enlarged sinus pudendus. In such a case, of good development of instincts and mental make-up and poor development of physical structures, it seemed to me that the individual should be classed on the side of the well-developed set of phenomena. Hence, I felt that the patient should be considered

When such conditions are present, the individual's inclinations and sexual desires ordinarily correspond with the male gonads, and in that case the classification as a male is correct. But in this case, the patient's instincts and preferences from childhood up, and the sexual desires and mental outlook of the present, were all strongly feminine.

This apparent sexual paradox made it necessary to determine if ovaries were present. Abdominal exploration was then carried out. This showed that there were no ovaries nor tubes nor uterus, the space between the bladder and rectum being entirely clear. With this operative revelation of no ovaries, the patient's earlier history became of special interest. During childhood there had been no departure from the ordinary activities of a girl. She went to the country school, got along very well with her studies, and associated with the other girls in their games. When not in school, she worked on the farm with the other children, doing her share of the heavy work. She always dressed and played as a girl. There were no tom-boy inclinations, nor desire for boys' clothes nor amusements.



Fig. 3.—Showing the enlarged clitoris and the perineal slit leading to the vestibule, and also the enlargement of the left labium by the testicle in it.

Pubic hair appeared at about fifteen years of age, but there was no menstruation. Sex desire towards men was noticed at age of eighteen or twenty. At about twenty, she had a slight pinkish discharge for three or four days. This was repeated four or five times, at intervals she thinks of about a month.

There was no more bloody discharge until about two years ago, when sexual intercourse began. Immediately after the first coitus there was a very free bloody discharge, which stopped the next day. Two weeks later there was profuse flow for some days, and five weeks later another short flow, but not so free. The last two flows came spontaneously, without coitus. Since that time coitus has taken place frequently, without any bleeding or pain or other disturbance, except that the vagina is very short. Her sexual desires have always been toward men, never shifting to women.

Here, then, was a patient with strong feminine instincts, sexual desires, and general outlook on life, but with testicles and no ovary. What sex classification should be made of such an individual? That

sponses of these patients. This is the other case in which the absence of ovaries was not confirmed by abdominal operation. But by deep palpation and the use of pneumoperitoneum, it was felt that ovaries were excluded with fair certainty.

Wharton:<sup>5</sup> Patient, aged 18, was of masculine build from the waist up and feminine build from the waist down. Had a beard. There was double inguinal hernia, hypertrophied clitoris and short vagina. On this diagnosis, the troublesome hypertrophied clitoris was removed and the hernia operation begun. In the hernial sac a testicle was found. An incision on the other side showed another testicle. The incisions were then closed, and later it was explained to the patient that a serious mistake had been made in amputating the supposed enlarged clitoris, which was in fact a penis, and that she was not a female but a male with two testicles. But the patient took quite a different view of the situation. She stated that no mistake had been made in amputating the enlarged clitoris, that she knew she was a woman and that she intended to live as such, and insisted on removal of the testicles. The testicles were finally removed, and abdominal exploration showed no ovaries. Improved adjustment. Normal libido. The patient married and sexual intercourse was satisfactory on her part and also on the part of the husband, except that the vagina was short. It was lengthened later.

Young:<sup>5</sup> Patient, aged 21, masculine build, but no beard. Lumps in the groin, no vagina. Patient was engaged to marry. Abdominal exploration showed no ovaries, tubes, or uterus. A vagina was constructed and the inguinal testes were put back in the pelvis instead of being removed. Improved adjustment. Normal libido.

Novak:<sup>2</sup> Patient, aged 19, masculine build, beard, hypertrophied clitoris, short vagina. In this case pelvic palpation showed bodies in the position of the ovaries, and about that size. Abdominal operation showed these bodies to be testicles in the usual position of ovaries and with a rudimentary broad ligament, but no ovaries, tubes, or uterus. The abdominal testes and the hypertrophied clitoris were removed. Improved adjustment. Normal libido. The vagina is to be lengthened later.

Our Case (for comparison). Patient aged 28, masculine build, beard, testicles in the groins, short vagina. Came for construction of vagina. Abdominal exploration showed no ovaries, tubes, or uterus.

It was clear then that those who had already struggled with the problem of the cases of this type had reached the same conclusion I had, namely, that the patient should be treated as a female. Some had reached this conclusion in the primary study of their patient, and others had been forced to it by later developments which confirmed and emphasized the predominance of the female element in the personality.

Having classified the patient as a female, with the right to live as such, the next step was to plan treatment to help as much as possible in that direction. The patient's two complaints were: first, the hair on the face which required frequent shaving and, second, the smallness of the vagina. So the two problems were to lessen the facial hair, by lessening the masculinity, and to lengthen the vagina. To accomplish these things, a combination treatment was planned consisting of (a) removal of the testicles, (b) administration of estrin preparations, and (c) stretching treatments for the short vagina.

Accordingly, I removed the testicles, doing the work under local anesthesia and checking each one with frozen section examination before removal, to exclude herniated ovary or ovotestis from removal. Later, Dr. Hobbs, in charge of the Laboratory, made a careful microscopic study of the testicles and there was no indication of ovarian tissue anywhere. As usual with retained testicles, there was no sper-

as primarily and essentially a female, and that our advice and treatment should be directed accordingly.

Now, could any substantial support be found for thus classifying and treating as a female, a patient with testicles and no ovary? The decision was a serious matter, for on it rested the direction of the future life-activities of the individual. Also, the decision had to be made promptly, as the patient was recovering from the abdominal exploration and was about ready for the further surgical work required.

In the short time available, I found records of seven comparable cases, that is, of cases in which predominant female sex desires and preferences persisted in the presence of testicles without an ovary. Of course, there are many other reported cases of this type, but these seven cases had been handled in recent years, under the present fund of knowledge concerning endocrines and sex determination, and hence their handling was studied with particular interest.

In these seven cases, the absence of ovaries was confirmed by abdominal exploration in five, and seemed fairly certain in the other two. The testicles were removed in six cases, and in the other case they were shifted from the groin to inside the pelvis. The hypertrophied clitoris was removed in four cases. In all of the patients operation was followed by improved social and sexual adjustment and continuation of normal libido. The essential details of these reported cases applying to our problem, were briefly as follows:

CASE 1.—(Mishell.<sup>3</sup>) Patient, aged 35, was of feminine build, but had never menstruated. She came for treatment for tender lumps in the groins. Examination showed double inguinal hernia with a testicle in each. External genitals were normal, with vagina represented by a small canal three inches long ending bluntly with no cervix.

Abdominal exploration showed no ovaries, tubes or uterus. The testicles were removed, and the hernias repaired. Improved adjustment. Patient returned to her work. Normal libido.

CASE 2.—(Mishell.<sup>3</sup>) Sister of preceding patient, aged 23, feminine build, complained of tender lumps in groins. Abdominal exploration showed no ovaries, tubes, or uterus. Testicles were removed. Improved adjustment and patient continued with good health. Headache which had troubled her disappeared after the operation.

CASE 3.—(Mishell.<sup>3</sup>) Sister of the preceding, aged 32, had lumps in the groins and had never menstruated. Examination showed the same conditions in this sister as in the other two. Feminine build, good breasts, no hirsutism, and instincts and feelings all feminine. The only thing special was that she became gray in childhood at the age of nine. The patient was well-adjusted, emotionally stable, had no complaint, and no operation was required. This was one of the two cases in which the absence of ovaries was not confirmed by abdominal operation, but careful pelvic palpation along with the similarity to the other two sisters excluded ovaries with fair certainty.

Rubovitz:<sup>4</sup> Patient, aged 39, masculine build, beard, testicles in groins, hypertrophied clitoris, short vagina, came complaining of severe libido and painful erections. The testes and the hypertrophied clitoris were removed, and the short vagina lengthened. There was improved adjustment and normal libido. The relief from the annoying erections was probably due more to removal of the enlarged and hypersensitive clitoris than to removal of the testicles, for as pointed out later the removal of the testicles seems to exert no influence on the sexual desires and re-



## CANCER OF THE CERVIX COMPLICATING PREGNANCY

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THE purpose of this paper is to report a case of cancer of the cervix complicating pregnancy, and by a search of the literature to determine if possible how much danger there is to the baby from exposure to radium during intrauterine life.

This condition is rare, occurring about once in 1,500 pregnancies, and the reason for this rarity is evident because usually cancer is a disease of later life or at least of the late childbearing age, whereas pregnancy is more common in younger women.

There is a tendency in many papers to discuss whether cancer of the cervix is a complication of pregnancy or pregnancy a complication of cancer, that is whether cancer antedated the pregnancy or developed after conception. Many writers argue that the diseased cervix tends to militate against conception. In the majority of the cases collected, cancer was not diagnosed until the second half of pregnancy.

Another academic controversy which seems to interest many writers is whether the coexisting pregnancy inhibits or accelerates cancer growth. This was not a major point in the research, but it was given consideration. However, the information obtained from most reports is thought to be insufficient to throw any light upon the controversy.

It would seem that expert knowledge is not a requisite for making a diagnosis; rather that thoroughness in examination, speculum visualization at the first prenatal visit and particularly the history of bleeding at any time during pregnancy, are of prime importance. In 5 of the cases of gross abnormalities of the baby, the reports stated that x-ray or radium was used for bleeding or for fibroid tumor in the first or second months of gestation, pregnancy not having then been diagnosed. These reports were all before the time of the Aschheim-Zondek test but nevertheless were evidence of gross carelessness, and they were all published in x-ray, not obstetric, journals.

In a consideration of the treatment we are confronted with a perplexing problem. In general it would seem, as in most all surgical complications of pregnancy, a good policy to treat the complication regardless of the pregnancy. The more or less commonly accepted present-day treatment of cancer of the cervix in the nonpregnant woman is radium, but it is also more or less commonly believed that radium treatment of cancer of the cervix in pregnancy is attended with grave risk to the baby. Study of Tables II and III would seem to lead one to believe that this danger is exaggerated. Such would seem to be true where treatment is not instituted until the second half of gestation; of 14 cases reported in this category, only one resulted in an abnormal baby and in

matozoa formation. At the preceding abdominal exploration, Dr. Sanford made a critical palpation of the kidney areas and could find no indication of adrenal tumor.

Systematic stretching treatments for the vagina are being employed. If sufficient lengthening cannot be secured in that way then operation is to be carried out. Estrin administration is being pushed with the double purpose of lessening the facial hair, by diminishing the masculinity, and of aiding the vaginal stretching by softening the pelvic tissues.

Various details discussed must be omitted here for lack of space, but it may be stated that in this case and in the reported cases the absence of ovaries and the presence of testicles seemed to exert little or no influence on the strong female desires and responses. Despite the hindering presence of testes and later the lack of sex glands altogether, the patient's feminine personality continued the even tenor of its way.

An important point in taking care of such a patient is to avoid terms or expressions which may disturb her psychologic balance by making her uncertain as to her sex. All records and explanations and reports should be made to conform to the correct primary sex, as worked out by careful study of the case. The patient is already disturbed by the malformation which she wishes corrected, but as a rule she has no thought that she may not be a woman, and it is strongly inadvisable to put her further adrift on the sea of uncertainty by branding her as a male according to the old superficial structural classification.

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UNIVERSITY CLUB BUILDING

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Kuschtalow, N. J., and Terentjewa, N. D.: The Influence of Chemical and Biological Factors on the Microscopic Picture of Milk and Colostrum, Arch. f. Gynäk. 165: 335, 1938.

The transition of colostrum into breast milk is produced by the direct effect of hormonal stimulation. Such stimulation arises in the pituitary, causing a degeneration of the colostrum bodies which become confluent and produce the fat globules of breast milk. Experimentally, this change from colostrum bodies to fat bodies is hastened in vitro by pituitrin, and in vivo it increases the fat contents of the milk. The activation of the secretory glands of the breast also hastens this transition. The authors were unable to produce any changes in the colostrum by the addition of any other hormones, ferments, sera, urine, or various chemical agents which were tested. The urine of pregnant women, however, did produce a characteristic microscopic change in the appearance of the colostrum bodies.

RALPH A. REIS

TABLE III. PATIENTS WITH NORMAL BABIES

AUTHOR	AGE	PARA	DIAGNOSIS	GESTATION	TREAT- MENT	DELIVERY
14. Neill, W., Jr.	32	Mult.	Cancer of cervix	5 months	Radium	Cesarean section
14. Neill, W., Jr.	21	Mult.	Cancer of cervix	6 months	Radium	Cesarean section
14. Neill, W., Jr.	28	Mult. colored	Cancer of cervix	7½ months	Radium	Cesarean section and supravaginal hysterectomy
15. Smith, F. R.	36	Mult.	Cancer of cervix	6½ months	Radium	Cesarean section, 8 months
16. Fagioli, M.	28	Mult.	Cancer of cervix	6 months	Radium	Cesarean section
17. Amico-Roxas, S.	27	Mult.	Cancer of cervix	6 months	Radium	Cesarean section and hysterectomy
18. Zimmerman	33	Mult.	Cancer of cervix	5 months	Radium	Normal confinement
19. Paroli, G.	29	Prim.	Cancer of cervix	3 months	Radium	Normal confinement
20. Van Rooy, A. W.	41	Mult.	Cancer of cervix	4 months	Radium	Normal confinement
21. Berkeley, C.	34	Prim.	Cancer of cervix	6 months	Radium	Cesarean section
22. Brouha, M., and Gosselin	31	Mult.	Cancer of cervix	6 months	Radium and x-ray	Cesarean section
23. Condamin, R.	38	Mult.	Cancer of cervix	5 months	Radium	Spontaneous normal confinement
24. Couvelaire			Cancer of cervix	5 months	Radium	Cesarean section, 8½ months
25. Povey	34	Mult.	Cancer of cervix	3½ months	Radium	Spontaneous normal confinement
26. Hoffman, H.	27	Mult.	Cancer of cervix	5 months	Radium	Normal confinement
27. Kane, H. F.	41	Prim.	Cervical polyp	3 months	Radium	Cesarean section*
28. Herold, K.			Cancer of cervix	5 months	X-ray and radium	Spontaneous normal confinement
29. Lacomme	39	Mult.	Fibroid	4 months	Radium	Normal confinement
29. Lacomme	39	Mult.		3 months	Radium	Normal confinement
30. Titus, E. W.		Mult.	Cancer of cervix	5 months	Radium	Normal confinement
31. Mundell, J. J.	33	Mult.	Cancer of cervix	6 months	Radium	Classical cesarean section

\*Baby was stillborn but no gross abnormality.

More often however the cancer is likely to be too far advanced for such a choice and many writers have suggested radium treatment followed shortly afterward by emptying the uterus, fearful of letting the pregnancy continue because of the great damage to the baby. Objection is offered to this plan because it is conceivable that operative manipulation on such a diseased cervix at this stage of gestation would too greatly endanger the life of the mother from sepsis or

that it is questionable whether radium was the cause of the abnormality. Some of the defects most likely were congenital and must have existed before the time of the treatment.

The problem then really revolves upon what to do with the condition when seen during the early months of pregnancy. Judging from this study this is indeed a rarity; in the whole series there are only 13 cases reported. In such a situation should one be fortunate enough to consider the cancer to be early, hysterectomy might be performed, with radium or x-ray preceeding or following the operation.

TABLE I. MISCARRIAGES

AUTHOR	AGE	PARA	GESTA-TION	DIAG-NOSIS	TREAT-MENT	RESULT
1. Zimmerman					Radium	3 patients miscarried shortly after radium given in middle of pregnancy
2. McGlinn	31		3 months	Cancer of cervix	Radium	Miscarried four weeks later
3. Tropea-Mandalari	40		3 months	Cancer of cervix	Radium	Miscarriage
4. Brouha						7 patients treated in early months followed shortly afterward by miscarriage
5. Mundell, J. J.	29		2 months	Cancer of cervix	Radium	Miscarriage

TABLE II. PATIENTS WITH ABNORMAL BABIES

AUTHOR	AGE	PARA	DIAG-NOSIS	GESTA-TION	TREAT-MENT	DELIVERY	RESULT
6. Aschenheim, E.	37	Mult.	Myoma	Early	X-ray	Normal confinement	Gross abnormalities, mentally deficient
7. Stettner, E.	41	Mult.	Myoma and bleeding	8 months	X-ray	Normal confinement	Gross abnormalities, mentally deficient
8. Abels, H.	34	Mult.	Metrorrhagia	Full term	X-ray	Normal confinement	Microcephalus
9. Schaab, A.	40	Prim.	Fibroma	Early	X-ray	Cesarean section	Microcephalus
10. Ries, E.	24		Metrorrhagia	4 months	X-ray	Spontaneous labor	Stillborn hydrocephalus. Absence right kidney. Latter antedated treatment
11. Goldstein, L., and Murphy, D. P.			Cancer of cervix	6 months	Radium	Normal spontaneous labor	Mentally defective
12. Gal, F.			Cancer of cervix		X-ray	Spontaneous labor	Microcephalus
13. Petenyi, G.			Cancer of cervix	Fifth to seventh month	X-ray	Spontaneous labor	Microcephaly and eye damage

In 6 of this group, treatment was given during the first half of pregnancy, and in 15 during the fifth and sixth months.

In 11 of this group the labor was normal, in 8 cesarean section was performed and in only 2 was cesarean section followed by hysterectomy.

Of 42 cases collected, 21 patients or 50 per cent, had normal babies, 8, or 19.04 per cent, had abnormal babies, and in 13, or 30.96 per cent, miscarriage followed shortly after the treatment.

Nine of these children were reported to be normal at the following ages: 2 years, 2 years, 3 years,  $3\frac{1}{2}$  years,  $4\frac{1}{2}$  years, 5 years, 8 years, 14 years, 20 years.

The last, 20 years old, reported by Sir Comyn Berkeley, is a girl who at the age of 15 broke the Olympic high jump record.

#### COMMENT

Radium to the cervix in the early months of pregnancy may be attended with risk to the baby, but in the second half of pregnancy, study of this series would lead one to the conclusion that the treatment is not as hazardous as heretofore believed.

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Miller, Norman F., and Todd, Oliver E.: Conization of the Cervix, Surg. Gynec. Obst. 67: 265, 1938.

Electrosurgical conization of the cervix is many times faster, simpler and a bloodless substitute for the Sturmdorf operation. The amount of tissue removed can be controlled and conization equals in efficiency any means of cervical gland reaming now available. Ultimate healing is but little slower than in the Sturmdorf procedure and the incidence of severe stricture probably not greater. In general, its use should be limited to women past the childbearing age and even in this group should not be looked upon as a substitute for the less radical office procedures now in use in the treatment of simple cervical disease. Conization is a desirable, quick, and convenient method of treating the cervix prior to subtotal hysterectomy.

WILLIAM C. HENSKE.

hemorrhage. Should one wish to adopt such a course, probably the safest method would be by abdominal hysterotomy.

It would seem, in view of the study of the cases reported in this series, that one might have a third choice. That would be, to give a smaller dose of radium, hopeful that it would, at least for the time being, retard the malignant growth and at the same time not be too hazardous to the baby; this to be followed by the customary radium dose after the pregnancy had advanced midway.

#### CASE REPORT

Mrs. G. S., aged 33 years, para vi, had had all normal pregnancies and labors, youngest child aged 6 years, other history irrelevant and no family history of cancer. The patient was a well-developed, well-nourished woman, first seen in the dispensary at Georgetown Hospital May 27, 1938. Last menstrual period Dec. 21, 1937. Expected date of confinement Sept. 28, 1938. Patient stated that she felt well during pregnancy until April 12, when, while moving heavy furniture, she believed she strained herself, as she experienced dull pain in the back and lower abdomen. The pain continued upon any exertion. On May 26 she fell in a sitting position and the next day passed two large blood clots, and on May 28 she came to the maternity clinic fearing that she would abort. Examination revealed the fundus at the level of the umbilicus, fetal heart 130 in left lower quadrant, and speculum examination showed an ulcerated craterlike area on the posterior lip of the cervix. She was admitted to the Hospital June 8 when a biopsy was performed and the pathologic report was as follows:

"Microscopically the section presents one large area of densely packed, markedly anaplastic stratified epithelial cells. These cells are very irregular in size and shape and there are numerous mitotic figures, some in multipolar division. The deeper underlying tissue has a dense infiltration of lymphocytes.

"*Diagnosis:* Squamous cell carcinoma, Grade IV."

The treatment consisted of 50 mg. of radium applied to the cervix for thirty-six hours each application, on June 12, 22, and 27, a total of 5,400 mg. hours.

From the time of the treatment until a classical cesarean section was done on September 15, thirteen days before the expected date of the confinement, she complained frequently of dull aching pain in the lower abdomen relieved somewhat by mild sedatives. At no time did the pain simulate labor pains.

On September 15 a classical cesarean section was performed, and the puerperium was uneventful. The baby, a male, weighed 6 pounds 11 ounces and the pediatric service reported that so far as could be ascertained the baby was normal. April 18, 1939: The baby is developing as a healthy normal child.

Analysis of the cases collected from the literature is as follows:

All but four women were multiparas. There were 13 cases in which miscarriage followed the application of radium during the first three months of gestation and 3 cases where it followed radium treatment in the middle of pregnancy.

There were 8 patients treated with x-ray or radium with grossly abnormal babies. Of these there was one patient with cancer who was treated with radium at the sixth month. Two patients with cancer were treated with x-ray, one at the fourth month and the other between the fifth and seventh months. The other 5 were treated for myoma or for metrorrhagia, all with x-ray. Two were in the early months, one at the fourth month, one at the eighth month, and one at term. It is questionable that x-ray therapy at the eighth month and at term was the cause of fetal abnormalities. The wisdom of treating these 5 cases of bleeding with x-ray is certainly questionable. All 8 patients in this category had spontaneous deliveries.

In 21 patients treated with radium the babies were normal. Nineteen of these cases were for cancer of the cervix, one for fibroid and the diagnosis was not given in one.

TABLE I. CLINICAL EVIDENCE OF SYPHILIS OR SUSPICIOUS HISTORY

CLINICAL EVIDENCE OF SYPHILIS AT FIRST VISIT			SUSPICIOUS HISTORY		
	NUM- BER	PERCENT- AGE OF 969		NUM- BER	PERCENT- AGE OF 969
Primary but no secondaries	5	0.31	History of lesion possibly primary No history of generalized eruption	44	4.54
Secondaries but no primary	13	1.34	No history of primary but rash possibly secondaries	38	3.92
Primary and secondaries	10	1.03	History of lesion possibly primary and history of skin eruptions possibly secondaries	19	1.96
Tertiary lesions	2	0.20	History of abortion or stillbirth	336	34.67
Evidence of congenital syphilis	15	1.54	History of infant deaths	74	7.63
Total	43	4.44	Total	511	52.73

There was one patient who presented herself at the clinic in the fifth month of pregnancy, whose blood Wassermann was negative and who presented no clinical evidence of syphilis nor did her history in any way suggest a possibility of syphilitic infection. This woman was delivered at term of a syphilitic baby whose Wassermann was strongly positive. The mother's Wassermann at delivery was also strongly positive. This patient was apparently infected during pregnancy and although she was examined at bi-monthly intervals at the clinic throughout her remaining pregnancy, no primary nor secondaries were observed either by the patient or the physician. This case supports the opinion that pregnancy may suppress primary and secondary manifestations of syphilitic infection.

#### QUESTIONABLE SYPHILIS

There is a variance of opinion as to whether or not pregnancy may produce a positive blood Wassermann reaction in women who are not syphilitic. Many clinicians with vast experience believe the blood Wassermann in pregnancy to be just as dependable as it is in the nonpregnant patient.

There was a relatively small number of women who presented themselves at the clinic who gave no history of syphilitic infection, no clinical evidence of syphilis, and who at their first visit had a weakly positive blood Wassermann. These patients were requested to bring their husbands and any former children to the clinic for examination and blood study. In those cases in which the husband and children gave no clinical nor serologic evidence of syphilis, the pregnant woman was not treated but returned for blood Wassermann examination each week for four weeks and then every second or third week for the remaining term of pregnancy. There were 65 of these patients set aside for study. The blood Wassermanns of these patients were observed to fluctuate from weakly positive to negative. The majority would have one weakly positive Wassermann followed by several negative reactions and then another weakly positive test. Many of them would have only one positive Wassermann and the remaining blood studies would be negative. The patients in this group were instructed to return with their babies six weeks after delivery for examination. Table II shows that 21 of these patients failed to return after delivery so were deducted from the study. Of the 44 who did return, 41 mothers and their babies had negative blood Wassermann reactions, which remained negative as long as it was possible to follow them. Nor was there any clinical evidence of congenital syphilis in the infants. Of the remaining 3 cases in this group, one mother and her infant both had strongly positive Wassermann reactions and were both placed upon treatment. Another of these women had a weakly positive blood Wassermann

# A REVIEW OF THE RECORDS OF SYPHILITIC PREGNANT WOMEN TREATED AT THE LOS ANGELES MATERNITY SERVICE OVER A TEN-YEAR PERIOD

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OF THE numerous studies that have been recently made of syphilis in pregnancy, the most exhaustive and detailed have been those of the Cooperative Clinical Group.<sup>1</sup> The very abundant clinical material at the disposal of this group for study makes their reports and opinions authoritative.

In the various clinics designated to the treatment of syphilis in pregnant women there are many factors peculiar to the individual clinic which must be considered in determining the type of treatment that is apparently best suited to the individual clinic.

The following study was undertaken with the intention of presenting the problems peculiar to the treatment of syphilis in pregnant women who presented themselves at the Los Angeles Maternity Service over the period of the past ten years, with an attempt to evaluate the form of treatment given them.

## MATERIAL STUDIED

The total number of patients who were cared for at the Los Angeles Maternity Service over this period of time was 35,594. Of this number of pregnant women 969 were found to have syphilis. This incidence of 2.04 per cent is quite low in comparison to studies made in other similar clinics. Race seems to be an important factor in determining the incidence of syphilis in clinical patients. In this clinic approximately 50 per cent are Caucasian women, approximately 35 per cent are Mexican women, and the remaining 15 per cent are negroes.

## CLINICAL EVIDENCE OF SYPHILIS OR SUSPICIOUS HISTORY

Table I demonstrates that of the entire group of 969 syphilitic pregnant women there were 3 patients, or 0.31 per cent, who had primary lesions but no secondaries when they first presented themselves at the clinic. There were 13 patients or 1.34 per cent who had secondary eruptions but in whom no primary lesion was found. There were 10 patients or 1.03 per cent who had primary and secondary syphilis at their first visit to the clinic. Two patients, or 0.20 per cent, presented tertiary lesions. There was clinical evidence of congenital syphilis in 15 patients, or 1.54 per cent. Thus there were 43 pregnant women, or 4.44 per cent, of the entire 969, who had clinical evidence of syphilis at the time of their first visit to the clinic.

In taking the history of each patient at her first visit it was found that 44 women, or 4.54 per cent, gave histories of a lesion possibly primary and no history of a generalized eruption that might be interpreted as secondaries. There were 38 patients, or 3.92 per cent, who gave a history of eruption possibly secondaries, but no history of lesions that might have been considered primary. There were 19 women, or 1.96 per cent, who gave histories of lesions possibly primary and eruptions possibly secondaries. There were 336 women, or 34.67 per cent, who gave histories of abortion or stillbirth, and there were 74 patients, or 7.63 per cent, who gave histories of infant death. Thus there were 511 women, or 52.73 per cent, who gave histories suspicious of syphilitic infection.



TABLE III. A COMPARISON OF OUTCOME OF PREGNANCY AMONG SYPHILITIC WOMEN TREATED AND UNTREATED DURING PREGNANCY

	NO TREAT- MENT		MINIMAL TREAT- MENT		MODERATE TREATMENT		MAXIMAL TREATMENT	
			LESS THAN 6 NEOARSPIHENA- MINE AND LESS THAN 10 HEAVY METAL		FROM 6 TO 10 NEOARSPIHENA- MINE AND 10 OR MORE HEAVY METAL		MORE THAN 10 NEOARSPIHENA- MINE AND MORE THAN 10 HEAVY METAL	
	NUM- BER	PER CENT	NUM- BER	PER CENT	NUM- BER	PER CENT	NUM- BER	PER CENT
Total patients	16		264		149		84	
Disastrous ter- mination of pregnancy (abortion or stillbirth)	2	12.5	20	7.5	9	6.04	0	0
Living syphilitic infants	11	68.75	53	20.07	21	14.1	6	7.14
Satisfactory ter- mination (liv- ing nonsyph- ilitic infants)	3	18.75	191	72.35	119	79.86	78	92.86

minimal treatment refers to less than 6 intravenous treatments of neoarsphenamine and less than 10 intramuscular injections of heavy metal. Moderate treatment designates patients who received from 6 to 10 intravenous treatments of neoarsphenamine and 10 or more intramuscular injections of heavy metal. Maximal treatment refers to patients who received more than 10 treatments of neoarsphenamine and more than 10 injections of heavy metal.

#### NO TREATMENT

There were 16 pregnant syphilitic women who failed to return for treatment before delivery. Of these patients 2, or 12.5 per cent, delivered stillborn infants. Eleven of these women, or 68.75 per cent, gave birth to syphilitic infants and 3 of these pregnancies, or 18.75 per cent, had a satisfactory termination: living, apparently nonsyphilitic infants.

#### MINIMAL TREATMENT

There were 264 patients who received less than 6 intravenous injections and less than 10 intramuscular injections of heavy metal. Of this group 20 pregnancies, or 7.57 per cent, terminated in abortion or stillbirth, 53, or 20.07 per cent, resulted in syphilitic infants, and 191, or 72.35 per cent, produced living, apparently nonsyphilitic infants.

#### MODERATE TREATMENT

There were 149 women who received from 6 to 10 intravenous treatments of neoarsphenamine and 10 or more intramuscular injections of heavy metal. Nine of these pregnancies, or 6.04 per cent, terminated in stillbirth or abortion, 21, or 14.1 per cent, resulted in living syphilitic infants, and 119, or 79.86 per cent, produced living, apparently nonsyphilitic infants.

#### MAXIMAL TREATMENT

There were 84 patients who received more than 10 intravenous treatments of neoarsphenamine and more than 10 intramuscular injections of heavy metal. None of these pregnancies terminated in abortion or stillbirth. Six of these patients, or 7.14 per cent, gave birth to living syphilitic infants, and 78, or 92.86 per cent, produced living, apparently nonsyphilitic infants.

TABLE II. APPARENTLY NONSPECIFIC POSITIVE WASSERMANN REACTIONS IN PREGNANCY

	NUMBER	PER CENT
Total patients studied	969	
Total patients in this group	65	6.71
Patients who failed to return for examination after delivery	21	2.17
Patients apparently syphilitic	3	0.31
Patients negative after delivery whose infants were also serologically and clinically negative for evidence of congenital syphilis	41	4.23

six weeks after delivery. Her infant had a negative blood Wassermann six weeks after delivery and presented no clinical evidence of congenital syphilis. This mother and baby failed to again return to the clinic. The third mother had a weakly positive blood Wassermann six weeks after delivery. Her infant presented no clinical evidence of congenital syphilis, the Wassermann reaction was negative six weeks after delivery and remained negative for the two years that he remained under observation. This mother took two years of treatment. Her blood Wassermann reaction continued to vary from negative to weakly positive during the two years that she was treated. It is possible that the behavior of this patient's Wassermann reaction was due to other causes than syphilis. Thus it was found in a study of 44 patients in this series whom it was possible to follow after delivery, that 41 apparently did not have syphilis. The incidence of apparently nonspecific positive blood Wassermann reactions in this group of pregnant women was therefore found to be 4.23 per cent.

#### TREATMENT

The great majority of patients who attend the Los Angeles Maternity Service do not present themselves until the fifth month of pregnancy or later. The problem therefore is to give these women as much treatment in the remaining weeks of pregnancy as the patient might be expected to tolerate, in an effort to secure a living nonsyphilitic infant. For this reason a combined scheme of therapy has been adopted.

As soon as the diagnosis of syphilis is established a course of treatment is outlined for each patient. Neoarsphenamine and a heavy metal\* are given in combination. The patient makes two visits to the clinic each week. The neoarsphenamine is given on Wednesday and the heavy metal on Friday. The patient is given a series of 6 to 8 weekly injections of neoarsphenamine (increasing from 0.15 to 0.45 gm.). For the past three or four years the policy has been to continue the heavy metal without interruption throughout the remaining weeks of pregnancy. After 6 to 8 injections of neoarsphenamine the patient remains on heavy metal alone for four weeks. A blood Wassermann is then taken and another course of neoarsphenamine is given. Following the suggestion of the Cooperative Clinical Group an attempt is made to arrange the courses of treatment in such manner that the patient receives intravenous arsenical treatments for several weeks prior to delivery. The urine is examined twice monthly and the percentage of patients who have not tolerated this scheme of therapy has been found to be so small as to be practically negligible.

Of the 969 syphilitic women treated during pregnancy at the clinic for the ten-year period, 453 failed to return to the clinic with their babies after delivery for physical examination and blood study and so were deleted from this summary. From the records of the 516 who did return with their babies for physical examination and blood Wassermann examinations, the following study was made.

For the purpose of comparison of treatment results the entire group has been arbitrarily subdivided into minimal, moderate, and maximal treatment. In Table III,

\*When this department was established ten years ago mercury was used in combination with neoarsphenamine. For several years past, bismuth has practically supplanted mercury in the scheme of treatment.

## THE TREATMENT OF GONOCOCCAL VAGINITIS BY ESTROGENIC HORMONE

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THE original basis for the use of estrogenic hormone in the treatment of gonococcal vaginitis was the demonstration of the influence of the follicular ovarian hormone upon the vaginal mucosa.

Stockard and Papanicolaou<sup>1</sup> describe cyclic changes in immature rodents; Allen<sup>2</sup> in immature monkeys; and Mazer and Ziserman<sup>3</sup> in spayed rodents under stimulation of estrogenic hormones.

The description by Davis and Hartman<sup>4</sup> of the details of the changes in the vaginal mucosa in monkeys during the physiologic cyclic change is of considerable importance in understanding the results produced in gonococcal vaginitis by the use of estrogenic hormones. They demonstrated that during the cyclic change in the mucosa, the epithelium, under the influence of the follicular hormone, consists of the greatest number of epithelial layers in the midinterval of the menstrual cycle. The mucosa at that time is composed of an active basal layer, an inactive functional layer and, between the two, an intraepithelial zone of cornification which is known as Dierks' layer. Following ovulation, desquamation begins and proceeds by a crumbling away of the functional or the superficial layer. The basal layer is not, at any time, desquamated and in the adult, regeneration takes place as a result of proliferation of the cells in this layer.

It has further been demonstrated<sup>5</sup> that the vaginal acidity in the newborn female is high and that shortly thereafter, the acidity declines. This is thought to be due to the influence of the ovarian hormone carried over to the child from the mother, which influence is lost shortly after birth. A similar increase in vaginal acidity has been shown to take place under the influence of the follicular hormone when introduced into the immature monkey.<sup>6</sup> Lewis,<sup>7, 8</sup> utilizing these physiologic changes, was the first to employ the hormone in the treatment of children having gonococcal vaginitis. His results were reported as favorable. Brown,<sup>9</sup> TeLinde and Brawner, Jr.,<sup>10</sup> Huberman and Israeloff,<sup>11</sup> Miller,<sup>12</sup> Abrams,<sup>13</sup> Limper and Hieronymus,<sup>14</sup> Lewis and Adler,<sup>15</sup> Benson and Steer<sup>16</sup> have all reported successful results without subsequent changes in physiology or damage to any structure in the patients as a result of the hormone employed.

Phillips,<sup>17</sup> Nabarro and Signy,<sup>18</sup> Wrana,<sup>19</sup> and Witherspoon<sup>20</sup> did not have similar success and warned against the possible dangers in the use of estrogenic hormone.

In order to determine from our own experience the value of the estrogenic hormone in the treatment of gonococcal vaginitis, a study was undertaken in three of the Social Hygiene Clinics of the Department of Health. In all, 108 patients were treated and observed for a sufficient length of time to report results. Their ages varied from three weeks to fourteen years. The diagnosis, in every instance, was based upon the presence of purulent vaginal discharge and gram-negative intracellular diplococci in the smear. No cultural diagnosis was employed.

### THE SIGNIFICANCE OF A POSITIVE BLOOD WASSERMANN IN SYPHILITIC PREGNANT WOMEN

Table IV shows that of the 516 syphilitic pregnant women in this study 188 had negative blood Wassermann reactions. Of these 188 patients, 181, or 96.28 per cent, bore living, apparently nonsyphilitic infants. Two, or 1.06 per cent, of these pregnancies resulted in the birth of living syphilitic infants, and 5, or 2.66 per cent, terminated in abortion or stillbirth.

TABLE IV. THE SIGNIFICANCE OF A POSITIVE BLOOD WASSERMANN IN SYPHILITIC PREGNANT WOMEN

	PREGNANT WOMEN WITH NEGATIVE WASSERMANN'S		PREGNANT WOMEN WITH POSITIVE WASSERMANN'S	
	188		328	
Total patients in group	NUMBER	PER CENT	NUMBER	PER CENT
Disastrous terminations of pregnancy (Abortions and stillbirth)	5	2.66	27	8.23
Living syphilitic infants	2	1.05	89	27.13
Living nonsyphilitic infants	181	92.28	212	64.64

There were 328 of this group of 516 patients who had positive blood Wassermann reactions; of these 328 pregnancies, 212, or 64.64 per cent, terminated in the birth of living nonsyphilitic infants. Eighty-nine, or 27.13 per cent, resulted in the birth of living syphilitic infants, and 27, or 8.23 per cent, ended in abortion or stillbirth.

### SUMMARY

1. The incidence of syphilis in pregnant women who attended the Los Angeles Maternity Service of the period over the past ten years was found to be 2.04 per cent.

2. There were 4.44 per cent of the pregnant women in this study who presented clinical evidence of syphilis at their first visit to the clinic; 52.73 per cent gave histories suspicious of syphilitic infection.

3. Though the blood Wassermann is the chief reliance in the diagnosis of syphilis in pregnancy and frequently the only evidence of syphilitic infection, there were 41 patients, or 4.23 per cent, in this study in whom there was apparently a nonspecific positive blood Wassermann reaction at some time during pregnancy.

4. The chances of a satisfactory termination of pregnancy in a syphilitic woman are increased with the amount of treatment she is given in pregnancy.

5. A negative blood Wassermann is of great value in determining the probable outcome of pregnancy in a syphilitic woman treated in pregnancy.

The author wishes to acknowledge his indebtedness to Dr. Lyle G. McNeile, director of the Los Angeles Maternity Service, at whose request the department of syphilis in the clinic was established, for the inspiration derived from his enthusiasm and untiring interest in the work done in this department.

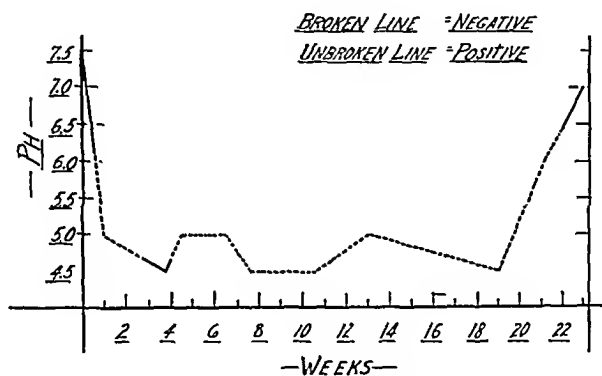
### REFERENCE

(1) Cole, H. N., Moore, J. E., O'Leary, P. A., Stokes, J. H., Wile, U. J., Clark, T., Parren, T., Jr., Vonderlehr, R. A., and Usilton, L. J.: Ven. Dis. Inform. Bull. 15: 83, 1934; 17: 39, 1936.

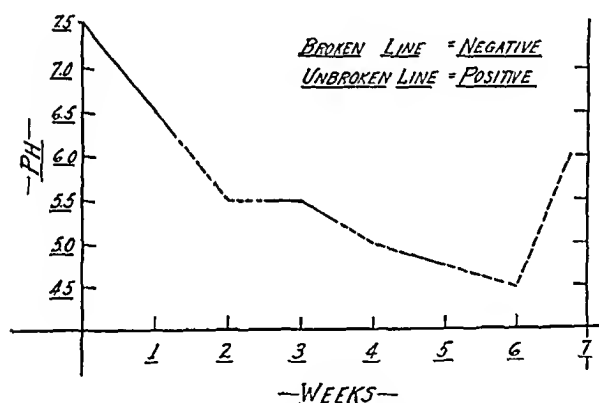
zine paper\*\* was used for pH determinations and proved to be quite satisfactory.

The combined results of smear examinations and the concomitant vaginal acidity readings are shown in Table III.

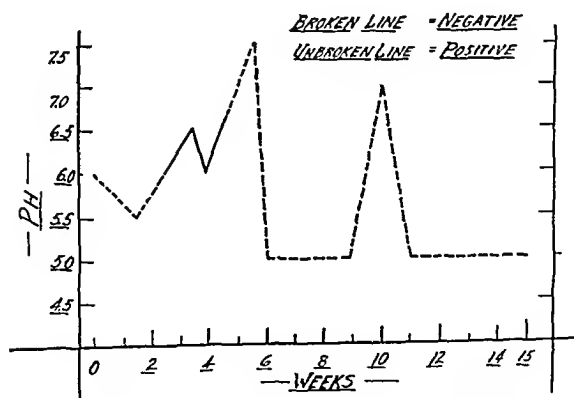
The smear reports in relation to vaginal acidity showed no consistent relationship as can be seen from Graphs 1 to 6.



Graph 1.—Vaginal pH smear relationship.



Graph 2.—Vaginal pH smear relationship.



Graph 3.—Vaginal pH smear relationship.

\*Nitrazine paper was supplied by E. R. Squibb & Sons.

## METHOD OF TREATMENT

Amniotin\* in capsules containing 1,000 international units was the medication employed. The mother was instructed in the clinic, by actual demonstration, in the method of using the capsules. After gently cleansing the external genitalia, the labia were separated and one capsule was introduced through the hymen into the vagina, just before bedtime. One capsule was introduced each night. No other treatment and no douches were employed.

## CRITERIA OF CURE

The patients continued under treatment until all clinical evidence of the disease disappeared. Smears at weekly intervals were taken in all cases. The determination of cure, however, was not begun until the clinical symptoms had disappeared. At this point, treatment was discontinued and numerous successive smears were taken for a period of two months. The minimum number of smears taken was six from each patient. If these smears were negative, subsequent observation, clinically and bacteriologically, was continued for six months thereafter. At the end of this time, the patient was discharged as cured, if all examinations were negative.

## RESULTS OF TREATMENT

Of the 108 patients treated, 92 appeared to be cured after a period of treatment varying from 14 to 435 days, the weighted average being 149.8 days. However, 24 of these patients relapsed in an average of 109 days, after being apparently cured. Sixteen patients were never cured. This makes it appear that 68 patients were permanently cured, so far as our observation of these cases went. The details of results in the various clinics appear in Tables I and II.

TABLE I. CLINICAL FINDINGS

CLINIC	NO. OF PA- TIENTS	NO. OF CURES	DURATION OF CURE (IN DAYS)			NO. OF RE- LAPSES	TIME OF RELAPSE (IN DAYS)			NO. OF CASES PERMA- NENTLY CURED
			EARLY	LATE	AVER.		EARLY	LATE	AVER.	
St. V.	20	16	53	95	75	3	41	56	49	13
C. H.	43	34	14	270	113	9	7	70	31	25
C.	45	42	35	435	208	12	45	270	183	30
Total	108	92			149.8	24			109.3	68

TABLE II. LABORATORY FINDINGS

CLINIC	NO. WITH NEG. SMEAR	TIME FOR NEG. SMEAR (IN DAYS)			NO. OF RE- LAPSES TO POS- ITIVE	TIME OF RELAPSE TO POS. (IN DAYS)			REMAIN- ING POSITIVE	POSITIVE REC- TALS
		EARLY	LATE	AVER.		EARLY	LATE	AVER.		
St. V.	13	30	64	48	3	7	485	51	4	4
C. H.	25	7	210	36	9	14	63	42	9	0
C.	30	5	120	23	12	8	252	72	3	9
Total	68			32.8	24			56.5	16	13

## THE INFLUENCE OF VAGINAL ACIDITY ON SMEARS

The acidity of the vaginal secretions was determined in our patients in relation to the presence of gonococci in the smear; 993 such observations were made. "Nitra-

\*The amniotin was supplied by E. R. Squibb & Sons.

## DISCUSSION

The favorable results, reported by various observers, produced by the use of the follicular hormone in gonococcal vaginitis have been attributed to the production of a mature type of vaginal mucosa following the administration of the ovarian hormone. This increase in the layers of vaginal epithelium is said to protect the tissues from penetration of gonococci and allow of the destruction by phagocytosis of the gonococci which have already penetrated into the submucosa. This explanation fails to take into consideration the fact that in every so-called gonococcal vulvovaginitis, the cervix is involved and that the cervical infection may, and often does, invade the parametrial lymphatic vessels.

While it is true that the cyclic change in the vagina occurs and that as a result of such cyclic change the discharge is diminished, no cyclic change has been irrefutably demonstrated in the cervical mucosa. This would tend to explain the number of patients who failed entirely to respond to hormone therapy.

The large percentage of relapses would indicate that phagocytic destruction of the gonococci in the submucosa does not occur in a large number of patients.

In addition, our experience in the adult female indicates that women may harbor the gonococci in the tissues for long periods of time without apparent evidence clinically or bacteriologically and nevertheless may act as sources of infection. It would, therefore, seem that the cyclic change in the vaginal mucosa cannot be advanced as the explanation of apparent cures.

The effect of the acidity on the life and growth of the gonococcus is too uncertain as demonstrated by the positive smears obtained in our series at pH levels of from 4.5 to 7.5. In addition, gonococci may be grown on culture media of a wide variety of acidity varying from 6.2 to 8.0.<sup>21</sup>

It would, therefore, seem that the explanation of apparently favorable results as being due to the increase of vaginal acidity resulting from the use of ovarian hormone which acidity inhibits and destroys the gonococci present is also doubtful.

The possibility remains that the disease in those who seem to be apparently cured may only be dormant and may relapse at some subsequent time. Such a possibility indicates the need for more thorough and exacting methods for determining cure in these patients.

The time required for apparent cure in our series is approximately the same as in our patients previously treated by other modalities.<sup>22</sup>

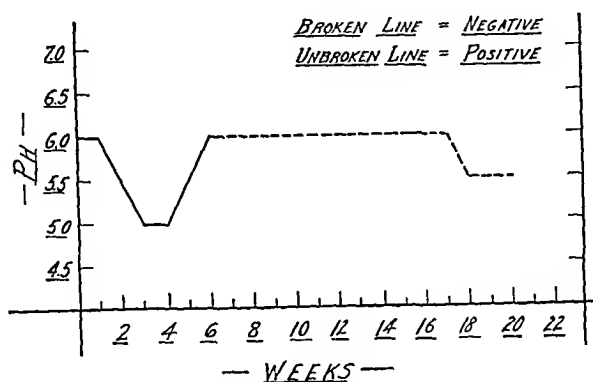
## SUMMARY AND CONCLUSIONS

1. One hundred eight patients were treated with amniotin in capsules containing 1000 international units inserted into the vagina every night.

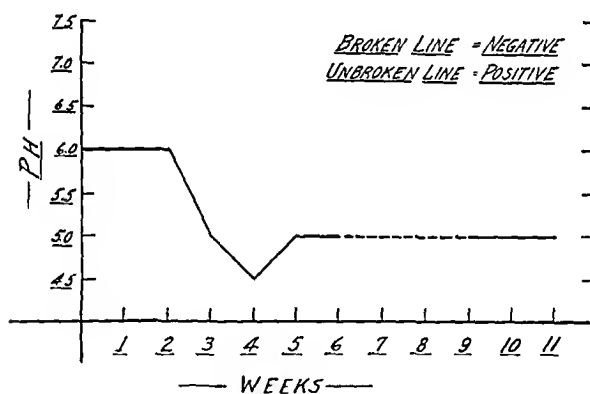
2. Ninety-two patients, or 85 per cent, were apparently cured. The average time required for cure was 150 days.

TABLE III. COMBINED REPORT OF CLINICS WITH 108 PATIENTS, FROM WHOM 993 SMEARS WERE TAKEN

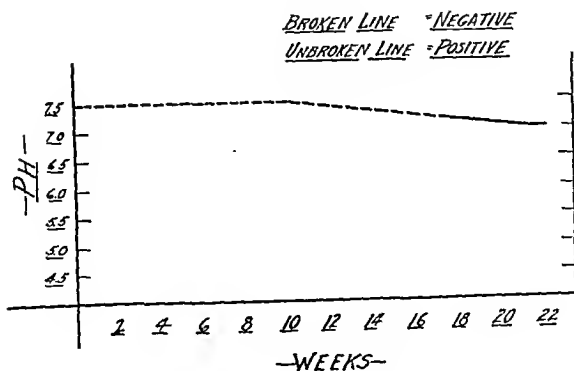
SMEAR	TOTAL NUMBER	pH VALUES	
		7.5-6.5	6.0-4.5
Positive	223	104	119
Negative	765	133	632
Doubtful	5	4	1



Graph 4.—Vaginal pH smear relationship.



Graph 5.—Vaginal pH smear relationship.



Graph 6.—Vaginal pH smear relationship.



## PREGNANCY ASSOCIATED WITH CHRONIC ULCERATIVE COLITIS

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MANY factors predisposing to infection of the colon by the organism of chronic ulcerative colitis (thromboleucorrhagial colitis) have been encountered. These have been discussed in previous publications.<sup>1,2</sup> Occasionally the infection has arisen in the course of an apparently normal pregnancy. Because of this, physicians have usually expressed great concern about pregnancy in the presence of chronic ulcerative colitis. As time went on, it was noted that some women, who became pregnant while active symptoms of the disease were at hand, experienced complete relief of symptoms of their colitis during the progress of their pregnancy. Frequently physicians dealing with such a combination of circumstances had thought it wise to end the pregnancy. Because of such experiences and the great anxiety generally apparent when the two conditions coexist, we felt that it would be of some interest to review the records of a series of patients who had become pregnant in the course of an active ulcerative colitis; or who had had ulcerative colitis, whose symptoms had become quiescent and who then had become pregnant. This is not a report of all of the patients who have come under our care or who have brought to our attention this combination of circumstances. It does, however, represent a series of patients who have been followed fairly closely.

Many women who have recovered from this most intractable illness have asked about the advisability of pregnancy. This question has frequently been asked months and years after recovery. It is well recognized that chronic ulcerative colitis is a disease of youth, and so when patients who have had the disease have become symptom-free and are married later, they have naturally experienced a concern about future childbearing. No one's experience with this combination of circumstances has been great enough to answer this question correctly. It was felt that a study of this series of cases might help us to answer the question more satisfactorily than before.

This series consists of only 17 women between the ages of 21 and 34 years. The 17 patients had 18 deliveries and 4 miscarriages (Table I). One of the patients is now pregnant and the symptoms have remained under control during the progress of her pregnancy, although the disease is not entirely quiescent. After 9 of the deliveries, the symptoms of colitis were improved (53 per cent). After 5 deliveries (29 per cent) the symptoms became worse. After 2 deliveries the symptoms of colitis

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3. Twenty-four patients, or 22 per cent, relapsed. The average relapse occurred in 109 days.

4. Sixty-eight patients, or 63 per cent, were seemingly permanently cured.

5. Sixteen patients, or 15 per cent, were unaffected and had persistently positive smears throughout the treatment.

6. The vaginal acidity showed great variations in relation to positive smears.

From the above, it would appear that although the treatment with amniotin capsules is simple and produces no apparent permanent physiologic damage, the results so far obtained are not conclusive. The uncertainty of the ultimate results with this treatment indicate the necessity for prolonged follow-up in those apparently cured.

The desirability of more intensive efforts to determine when cure is established is obvious, and investigation for this purpose along with other phases pertaining to this disease is urgently needed.

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Strassman, Erwin O.: *The Theca Interna Cone and Its Role in Ovulation*, *Surg. Gynec. Obst.* 67: 299, 1938.

Ovulation is a mechanical process stimulated by the endocrine glands. Based on more than 18,000 serial sections of ovaries from human beings and mammals, the following facts were ascertained:

Universally an eccentric growth of the theca interna of the growing follicle was found. This one-sided proliferation of the theca interna is always directed toward the surface of the ovary. It forms a cone which is wedge shaped on the cut surface, infiltrates and penetrates the surrounding tissues, thus making a path for the growing follicle.

The growing Graafian follicle ascends to the surface of the ovary by following the line of least resistance which is provided by the cone of the theca interna. A more or less marked degree of edema is present in the surrounding tissues, which facilitates the mechanical progress of the ascending follicle.

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colitis occurred. It is possible that we are dealing with a somewhat different form of the colitis in these cases. It seems more likely, however, that some product of metabolism is present in these cases in variable amounts. Perhaps there is a foreign protein reaction to such a substance, simulating the response to an allergen. After all, the cause or causes of the toxemias of pregnancy are by no means clear. Some have thought that rapid proteolysis in the chorionic villi of the pregnant woman leads to the formation of an antiferment; others have thought that there is a dislocation of the normal values in the blood of estrin, prolactin, and progesterone; still others have considered an unusual absorption of the split products of digestion from the intestinal tract; and others have thought of the early toxemia of pregnancy as a neurosis.

There seems little doubt that the protein requirement of the average patient suffering from chronic ulcerative colitis is not met, owing to interference with absorption as well as to failure of adequate intake.<sup>3</sup> These patients require increased intake of protein. The same can be said of pregnant women. The improvement in the cases of colitis reported here compares favorably with the improvement in those uncomplicated by pregnancy. The reaction to pregnancy is variable. That some recover completely during the period of gestation is of particular interest. Could the variability in protein intake and absorption offer a lead to an explanation of this phenomenon? Perhaps the intestine acts as an organ of elimination of the excess products of protein metabolism. If this were so, the excess of protein in the body might in turn react favorably on the colitis. Under such circumstances we should expect no effects in some cases. An overwhelming infection might explain the fact that some cases actually become worse after pregnancy. It must be said that a further study of such cases might open up a fruitful field of investigation into both of these problems.

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In both urban and rural areas there is an evident increase in hospitalization of maternity cases. If this trend is due to a belief that the hospital is a safer place for delivery than the home, then we must insure the truth of that belief. We can do this by proper isolation of the maternity department in all of its ramifications. That will minimize infection contacts.

By proper organization of our staffs and facilities we can reduce the hazards of hemorrhage, and by consultation, the hazard of obstetric trauma and operative risk. By education of the public and profession we can reduce the convulsive toxemias of pregnancy. By staff conferences we can measure our organization and our results and effect changes to continue to make our hospitals worthy of the increasing confidence of our maternity patients.

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were unchanged. After 1 delivery so little change was noticed that the patient was unwilling to express herself. In one instance, the symptoms of colitis began after delivery. Again after 2 (50 per cent) of the miscarriages, the symptoms of the colitis were definitely improved. After a third miscarriage the symptoms seemed somewhat improved and after a fourth miscarriage the symptoms were unchanged. An illustrative case history follows:

CASE 1.—A single woman, aged 25 years, from Ohio came under the care of the Mayo Clinic in November, 1934, with a history of bloody dysentery of two months' duration. At that time the proctoscopic picture was typical of that seen in the streptococcal type of chronic ulcerative colitis. The lesions were found to be limited to the rectum and sigmoid portions of the large intestine. The patient's general condition was otherwise satisfactory.

TABLE I. EFFECT OF PREGNANCY ON COLITIS IN 17 INDIVIDUALS WHO HAD 18 DELIVERIES AND 4 MISCARRIAGES

	COLITIS			
	IMPROVED	WORSE	STARTED	UNCHANGED
After delivery	9	5	1	3
After miscarriages	3			1

In spite of usual treatment, including the administration of vaccine, the patient's condition failed to improve but remained the same until her return in January, 1935. At that time a course of the anticolitis serum was given and soon progress was quite satisfactory. She became symptom-free and had been so for about a year when she was married. In January, 1937, pregnancy was noted. The bowel condition remained unchanged until the middle of May, 1937, when there began cramping and abdominal pains with the passage of five to six bloody rectal discharges daily. When the patient failed to improve on symptomatic measures, she was advised to have her pregnancy terminated. The condition of her bowels became slightly worse and she returned to the clinic in the seventh month of her pregnancy. She was hospitalized; treatment with serum was recommended. The usual program was outlined and the bowels gradually improved. By the time of an uneventful delivery at full term, the symptoms of colitis had entirely subsided. This was in October, 1937. The patient has had no further symptoms of her colitis up to this date.

#### COMMENT

Judging from a very large number of inquiries received about the risk of colitis complicating pregnancy, it is evident that there is no uniform opinion about the management and prognosis of these coexisting conditions. Many have thought that the association of pregnancy and chronic ulcerative colitis should be viewed much as tuberculosis and pregnancy are considered.

This series of patients presents an interesting problem. It cannot be said that the patients in whom good effects followed pregnancy were simply those in whom the colitis was milder. In all of them it was moderately severe, and several of the patients who recovered and who have never had a recurrence of the disease suffered from the fulminating septic type of ulcerative colitis. One of these women has had no sign or symptom of her former colitis for twelve years.

Again, it was in some of the less severe cases that no effect on the

TABLE I. RESULTS IN 25 TYPICAL CASES

CASE	PUERPERIUM DAY OF FIRST DOSE	NO. OF DOSES	PREPARATION	PARTY	DELIVERY	CHARACTER OF PUERPERIUM	RESULTS
1	4	4 × 2 c.c.	Anterior pituitary- ovarian	Primip.	Low forceps	Normal	All symptoms relieved after fourth dose
2	1	4 × 2 c.c.	Anterior pituitary- ovarian	Primip.	Cesarean section	Normal	No engorgement, no pain, no secretion
3	1	4 × 2 c.c.	Anterior pituitary- ovarian	Primip.	Normal	Normal	Breasts moderately full, but no pain and no secretion
4	1	4 × 2 c.c.	Anterior pituitary- ovarian	iv	Version and breech extraction	Normal	No engorgement, no pain, slight secretion
5	1	4 × 2 c.c.	Anterior pituitary- ovarian	Primip.	Anencephalic monster	Normal	Breasts firm for 1 day, but no pain, no secretion
6	6	4 × 2 c.c.	Anterior pituitary- ovarian	Primip.	Normal	Normal	No engorgement, no pain, no se- cretion
7	10	4 × 2 c.c.	Anterior pituitary- ovarian	Primip.	Normal	Acute mastitis. Cracked nipples	Slight engorgement, pain de- creased slightly, secretion stopped immediately
8	2	2 × 2 c.c.	Anterior pituitary- ovarian	Primip.	Normal	Poor breast tissue. Normal	Complete cessation of secretion, no pain
9	28	4 × 2 c.c.	Anterior pituitary- ovarian	ii	Normal	Cracked nipples, old scar and caked breasts	Immediate cessation of secretion, no pain
10	1	3 × 2 c.c.	Anterior pituitary- ovarian	ii	Cesarean section. Placenta previa	Normal	No engorgement, no pain
11	1	4 × 2 c.c.	Anterior pituitary- ovarian	i	High midforceps. Stillbirth	Normal	No secretion, no pain, no fullness
12	5	4 × 2 c.c.	Anterior pituitary- ovarian	ii	Normal	Cracked nipples, caked breasts	Immediate cessation of pain, se- cretion and fullness

## THE INHIBITION OF LACTATION DURING PUERPERIUM BY ANTERIOR PITUITARY AND OVARIAN EXTRACTS

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IT IS generally admitted that mammary growth and function are dependent upon hormones produced by the ovaries or by the anterior pituitary gland. A placental hormone also has been mentioned in this complex interrelationship. A delicate balance of hormonal stimulation and inhibition is important.

Kurzrok, Wilson, and Cassidy (1925) reported definite growth of the breasts by the use of large doses of follicular hormone. Vintenberger, Allen, Turner and others also found that estrone could stimulate growth of the mammary ducts, but they found that the corpus luteum hormone, progesterone, was necessary to bring about the hyperplasia of the lobules that also occurs during pregnancy. Nelson and Piffner in their experiments produced duct and lobule development with lipoid extract of sow's corpora lutea. Ancel and Bouin (1911), Lobe and Hasselberg (1917) and many others utilized aqueous lutein extracts without success.

It seems that if the aqueous ovarian extract of the whole ovary were used, one might obtain an antagonistic or galactophygous effect. For this purpose an ovarian extract\* containing no estrone or other estrogenic substance was tried.

Realizing the part that the anterior pituitary gland plays in the regulation of ovarian activity, we decided also to use a preparation containing both ovarian and anterior pituitary extracts.† It was our expectation that the anterior pituitary extract would increase or heighten the response produced by the aqueous ovarian extract. In doing so, we were not unaware of the experiments of Pencharz and Long (1933), Stricker and Greuter (1929), Gardner and Turner (1933), Bates and Riddle, Kurzrok and others who established that certain anterior pituitary extracts were galactotropic.

Our results with anterior pituitary-ovarian solution to date, in conditions where the inhibition of lactation was desirable, have been extremely gratifying. In one group of 25 cases, aqueous whole ovarian extract alone was used. In another group of 75 cases, anterior pituitary-ovarian solution was used. The cases selected included: (1) mothers who had stillbirths of long or short duration; (2) mothers in whom the death of the fetus took place during labor; (3) mothers in whom an attempt at lactation was not advisable (i.e., those with deformed nip-

\*Supplied by the George A. Breon and Co. Each cubic centimeter contains the extractives from 40 gr. ovarian whole gland from cattle.

†Each 2 c.c. contains extractives of 10 gr. of anterior pituitary glands and 40 gr. of ovarian whole gland from cattle.

ples); (4) mothers in whom it was advisable to stop lactation because of the dangers of threatening breast abscess. (This last group included patients with intractably sore nipples, stubborn cases of caked breasts, and cases of acute mastitis.)

In order to fairly evaluate these preparations we insisted that no other method be used that might influence our results. For this reason, we did not bind the breasts tightly, use ice bags, saline cathartics, sedatives, or restrict fluids in any of our cases.

Our treatment consisted of daily intramuscular injections of 2 c.c. of the respective extract on the first, second, third, and fourth days following delivery. In only one case was it necessary to give a fifth injection.

In the anterior pituitary-ovarian treated group, our results were good in 70 cases, fair in 3, and ineffective in 2. In the ovarian treated group (25), good results were obtained in 17 cases, fair in 5, and no effect was noted in 3 cases. It seemed that in the ovarian treated cases the amount of fullness of the breasts was a little more marked. Our observations in the anterior pituitary-ovarian series were as follows: (1) In no case was it necessary to give analgesic drugs to stop pain. (2) The nurses reported that none of these patients required help in turning because of engorged breasts. (3) The breasts were not as hard and as tense as they were under the old regime of ice bags, restricted fluids, saline cathartics, and breast binders. (4) The temperatures from engorged breasts were entirely absent. (5) No patient complained so severely that additional support of the breasts was necessary. (6) In two cases the breasts became full but the freedom from pain was remarkable.

The result on 25 typical cases are summarized in Table I.

This regime was used in three different hospitals by 15 unbiased clinicians. All observers spoke highly of this method; some stating that their results were excellent.

#### SUMMARY

No single preparation can be depended upon to give uniformly excellent results in bringing about a painless cessation of lactation. The combined extracts of the anterior pituitary and ovarian glands of cattle gave excellent results in at least 90 per cent of those treated. The results in a group of patients treated with ovarian extract alone were not as satisfactory as in the anterior pituitary-ovarian group, good results being obtained in only 68 per cent of the cases. While some engorgement of the breasts was noted in a few of the patients treated by these preparations, the freedom from pain is a prominent feature.

I am greatly indebted to Drs. Ferri, DiNorecia and Meinhard for their kind assistance in this study.

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13	2	4 x 2 c.c.	Anterior pituitary-ovarian	ii	Cesarean section. Placenta previa	Normal	No fullness, no pain, no secretion
14	4	4 x 2 c.c.	Anterior pituitary-ovarian	iii	Premature, normal	Painful and engorged breasts. Normal	Pain and fullness decreased
15	8	3 x 2 c.c.	Anterior pituitary-ovarian	i	Vaginal cesarean section	Engorged breasts. Acute mastitis	Pain disappeared, fullness decreased, secretion stopped
16	1	3 x 2 c.c.	Anterior pituitary-ovarian	i	Stillbirth (3 weeks)	Normal	No fullness, no pain, no secretion
17	1	3 x 2 c.c.	Anterior pituitary-ovarian	i	Low forceps	Normal	No fullness, no pain, no secretion
18	1	2 x 2 c.c.	Anterior pituitary-ovarian	i	Stillbirth (6 months)	Normal	No fullness, no pain, no secretion
19	1	4 x 2 c.c.	Anterior pituitary-ovarian	iii	Cesarean section	Normal	No fullness, no pain, no secretion
20	1	4 x 2 c.c.	Anterior pituitary-ovarian	ii	Bougie induction for hemoptysis (T. B.)	Normal. Hemoptysis stopped	No fullness, no pain, no secretion
21	5	4 x 2 c.c.	Anterior pituitary-ovarian	i	Low forceps	Caked breasts, cracked nipples	Immediate relief of pain and engorgement after first dose
22	1	3 x 2 c.c.	Anterior pituitary-ovarian	Primip.	Twin delivery; 1st fetus 8 mo. premature; 2nd fetus dead and retained in uterus 1 mo.	Normal	No secretion, no pain, no fullness
23	1	2 x 2 c.c.	Anterior pituitary-ovarian	i	Normal	Normal. Poor breast tissue	No secretion, no pain, no fullness
24	1	2 x 2 c.c.	Anterior pituitary-ovarian	i	Low forceps rotation. R.O.P.	Normal	No secretion, no pain, no fullness
25	4	4 x 2 c.c.	Anterior pituitary-ovarian	iii	Cesarean section. Placenta previa. Baby died on second day	Engorged breasts on fourth day	Immediate cessation of pain and secretion. Fullness for 2 days



lants of motility, such as glucose solution or Hirokawa's diluent (one part of 1/10 N sodium chloride solution and 100 parts of Ringer's solution) will not change the relation of their various motilities. Again, sperms deprived of oxygen are only sluggishly motile and lose practically all motility in a CO<sub>2</sub> environment.

It is evident that in the sperm reservoir of the male, that is, the epididymis, the sperms must be able to live for many days.

Hammond and Asdell<sup>6</sup> have shown in the rabbit after isolation of the tail of the epididymis sperm survival with retention of their fertilizing powers up to 40 days, and retention of motility up to 60 days. Young<sup>7</sup> found that under similar conditions in the guinea pig the spermatozoa retained their fertilizing powers for 25 to 30 days and their motility for 50 to 59 days, while White's<sup>8</sup> figures in rats were 21 and 42 days, respectively. However, the epididymis in the scrotum is at a lower temperature (2.5 to 7° C.) than the body itself, and when the gonads and epididymis are transplanted into the abdominal cavity, degeneration of the testicular tubules results and any form of heat whatever applied to the testes for any length of time has the same effect. Even the process of wrapping the scrotum in some impermeable substance like oiled silk will cause testicular tubular degeneration. However, the spermatozoa in the tail of the epididymis survive this heat insult much better than the testicular tubules. Thus, bathing the scrotum of a guinea pig with water at 46° C. for 30 minutes produced a severe testicular tubular degeneration, whereas the sperms in the epididymis remained fertile for 31 days afterward. Lawrence,<sup>9</sup> Moore,<sup>10</sup> Heller,<sup>11</sup> and Yochem<sup>12</sup> have shown that sperms in the scrotum of a guinea pig remained motile for 70 days and only 14 days in the abdomen. In the rat the figures were 30 days and 5 days, respectively.

Outside of the body the sperms of course live a much shorter time. At body temperature Hammond,<sup>13</sup> Walton,<sup>14</sup> and Hammond and Asdell<sup>15</sup> showed that rabbit sperms remained fertile only 13 to 14 hours. The sperms lived longest at 10° to 15° C., and even at 0° C. some lived 72 hours. Sperms taken from the vas deferens if kept cold could be kept fertile for as long as 7 days, whereas those from the vagina never more than 4 days. I myself have divided the same human serum ejaculate into three parts and kept all three parts under identical conditions, except that one was subjected to normal body temperature in the incubator, one was left at room temperature, and one was placed in the refrigerator at 10° C. All the incubator sperms were dead after 18 hours. Those at room temperature lasted about 36 hours (summer weather), and those kept in the ice box four to five and more days.

The obvious conclusions from the foregoing are that the sperms mature as they move along the tubular system of the testicle, rete, vasa deferentia and epididymis; that they are stored more or less immobile in the epididymis under a lack of oxygen and held in check further by strongly alkaline secretions; that the temperature is regulated by the scrotum and is always lower than the general body temperatures; that body temperature reduces the life of the sperms 75 to 90 per cent, and that the more mature the sperms, the sooner they die; that ejaculated spermatozoa in all animals investigated die in less than 48 hours when exposed to body temperature, providing oxygen is available; that the sperm withstands heat better if there is

## THE LONGEVITY OF THE HUMAN SPERMATOZOA

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THE mass of evidence showing that the spermatozoa of animals with extra-abdominal testes live but a relatively short time (forty-eight hours or less) at body temperature, and therefore an equally short time in the female genital tract, has assumed enormous proportions and is steadily increasing. Here and there, however, a dissenting voice is heard.

Huhner<sup>1</sup> reports taking sperms from the cervix many days after coitus and finding them motile under the microscope. Macomber<sup>2</sup> reports similar findings four and even seven days post-coitum, and Carey<sup>3</sup> reports progressively motile sperms removed from the cervix thirty-six to eighty hours after coitus. Carey also cites Stokes'<sup>4</sup> experiences after vasectomy and Nürnberger's<sup>5</sup> cases which he reported eighteen years ago in which the excised Fallopian tubes thirteen and fourteen days after the last reported (!) intercourse showed motile spermatozoa.

Of course patients often unconsciously and deliberately deceive their physicians in this question, but both Huhner and Carey, feeling that this was not true in their reported cases, think that their findings are a contradiction of the fact that sperms live but a short time in the female genital tract. The findings of these authors are however not at all at variance with the modern scientific view, but one must specify what is meant when one says that all the sperms are killed in the female genital tract in forty-eight hours or less. This statement of course applies to such sperms as are possibly concerned in fertilizing the ovum and meet normal conditions in the female genital tract. That some sperms may meet unusual conditions, or may be too weak to penetrate the cervical mucus is of no importance in this question, and certainly sperms still in the cervix after two to seven days have not met normal conditions, or are inherently abnormal in one way or another. To make this point clear, it is necessary to review our present knowledge of spermatogenesis as briefly as possible.

The sperms produced by the testes when they become free-swimming have a sluggish motility and are not mature. As they move along the rete and vasa deferentia to the epididymis they mature and become increasingly motile. This process continues until the sperms reach the tail of the epididymis. Here they are packed in like sardines and due to the lack of oxygen and the strongly alkaline secretion of the epididymis remain practically motionless. (The sperms are not stored in the seminal vesicles as was formerly believed. This I have pointed out repeatedly before.) Sperms taken from different parts of the ducts always exhibit varying degrees of motility depending on how far along the ducts they have journeyed. Even stimu-

# TEN CASES OF BRENNER TUMOR OF THE OVARY

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THE tumor is rare so far as reports in the literature are concerned, but all writers agree that it is only moderately so if routine gross and microscopic section of the ovary is performed. Bland and Goldstein<sup>2</sup> reported 66 cases in the literature to 1935, but since the indefinite terminology and the heretofore confusion with granulosa cell tumors and simple carcinoma make it quite probable that not all these cases were true Brenner tumors, the 24 cases to 1936 gathered by Proescher and Rosasco<sup>3</sup> may represent a truer picture. In addition, the following have recently published 11 cases: Frankl and Klatten<sup>4</sup> in 1934, 1 case; P. H. Smith<sup>5</sup> in 1935, 1 case; Sikl<sup>6</sup> in 1935, 2 cases; Bassal and Fabre<sup>7</sup> in 1936, 1 case; Gaines<sup>1</sup> in 1936, 4 cases; Proescher and Rosasco<sup>3</sup> in 1936, 1 case; and Gnassis<sup>8</sup> in 1937, 1 case.

The first seven of our ten cases were found by re-examination of all the microscopic sections of ovary in the pathologic files (since 1901, by G. V. S.), and the diagnosis was confirmed through the courtesy and cooperation of Dr. Robert Meyer, of Berlin, in 1934. Of these 7 cases 1 had been completely missed, 1 had been termed a fibroma, another simply "gland inclusions"; 2 had been diagnosed as early carcinoma, 1 as a fibrosarcoma, and 1 as a granulosa cell tumor. The last 3 cases encountered, since the consultation with Dr. Meyer, have been diagnosed without hesitation.

Table I graphically summarizes the findings, but the following facts deserve further note, though they have been mentioned in previous papers. Six of the 10 tumors were associated with cysts on the same and/or opposite side, and of these, 3 were benign multilocular pseudomucinous cystadenomas, 2 benign papillary serous cystadenomas (one early), and 1 was cortical, i.e., the ovary contained many cortical glands, some cystic. The apparently incidental finding of a Brenner tumor in a case of squamous carcinoma of the vagina with proclitelia was the only instance of association with malignancy in this series; no other indication of or association with malignancy has been found or published. Six of the remaining 9 tumors were also microscopic and entirely incidental, 1 being found in the wall of a multilocular pseudomucinous cyst; 3 were grossly the apparent pathology, being solid ovarian tumors 2 by 2 by 2, 7 by 5 by 5, and 10 by 8 by 6 cm. in diameter, respectively. Leiomyomas of the uterus were present in 5 cases; adenomyosis in 3. Three patients had had pelvic inflammatory disease but only 1 had known latent syphilis. Two patients were in the fourth decade, 4 in the fifth, 1 in the sixth, and 2 in the seventh. Two cases were postmenopausal without bleeding, 2 (1 with squamous carcinoma of the vagina, the other with polyps) were postmenopausal with recent spotting, 1 was without history, 1 had normal menses, and 4 had moderate to profuse increase of menstrual flow. All (9, one clinical history unobtainable) except 2 had had one or more children and both of these had had spontaneous abortions.

## CASE REPORTS

CASE 1.—Mrs. L. was operated upon on March 21, 1910. The patient was a private case and the clinical record is not available.

*Pathologic Report No. 2468, Gross:* The specimen consisted of a multilocular ovarian cyst 18 by 17 by 6 cm. without papillary formations. *Microscopic:* Sections of the cyst wall showed a high cylindrical epithelium in a single layer. In dense ovarian stroma there were several nests and islands of polygonal epithelial cells showing no signs of infiltration. A few of these nests were vacuolated to varying

a lack of oxygen and strong alkaline buffering secretions surround them; that motility is not a criterion of the fertilizing power of the sperm cell, and that motility is generally retained for a considerably longer period of time than fertilizing power.

If in this light we now consider the reports of Huhner, Carey and Macomber, it will be seen that sperm cells embedded in the cervical mucus will be suspended in a strongly alkaline medium, while little oxygen is available. Their motility therefore will necessarily be reduced or almost nil, as in the epididymis a potential motility may remain for days. When such sperms are placed under the microscope and oxygen becomes available they naturally may show active motility. That does not mean, however, that such cells are still fertile, and it certainly means that something is radically wrong; otherwise these sperms would be through the cervical mucus, not in a few days, but in a few hours. These reported sperm findings in the cervix after such long intervals post-coitum therefore are simply freaks which in no wise modify the well founded conclusion that the sperms (those to be considered as possibly causing pregnancy, if one wishes) are all killed off by the heat and environment of the female genital tract in less than 48 hours. Since in all experiments the sperms taken from the vagina always lived only about half the time of those from the vas deferens and the tail of the epididymis, the conclusions are obvious; namely, to evaluate properly the quality of a semen specimen it must not be taken from the vagina or cervix, but must be a fresh ejaculate kept cool. Of course if a condom is used, prompt removal from the condom should take place immediately after ejaculation, and preferably the condom should be held up and its closed end snipped with a scissors so that the semen comes into contact with as little rubber surface as possible, or a skin condom may be used. And even then a complete evaluation of a semen specimen can only be made if all the factors influencing spermatogenesis are thoroughly known and properly considered.

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degrees. *Diagnosis:* Multilocular pseudomucinous cystadenoma. This was later changed to include Brenner tumor and was confirmed by R. Meyer in 1934.

CASE 2.—Mrs. C. S., a 41-year-old white female, gravida i, para i, was admitted to the hospital on May 24, 1917, complaining of a bearing-down sensation in the vagina, pain in the left lower abdomen and lumbar backache, all symptoms having been present an indefinite time but worse in the past four months. The menstrual history was normal but the abdominal pain was exacerbated during menstruation. Pelvic examination revealed a cystocele, lacerated cervix, prolapse, fundus forward and of normal size, a tender mass in the left adnexal region, and the right adnexal region negative. Dilatation and curettage, anterior colpoplasty, perineoplasty, left salpingo-oophorectomy, appendectomy and fixation of the round ligaments were done. The patient reported herself well eleven years later.

*Pathologic Report No. 7007:* The curettings were grossly normal. The ovary measured 5 by 2 by 2 cm.; at one end there was a nodule 2 centimeters in diameter which appeared to be a fibroma. The endometrium was of the pre-menstrual type. The ovary showed the usual structure of a fibroma and scattered through it were small nests of epithelial cells with a few areas of calcification. *Diagnosis:* Pre-menstrual endometrium; fibroma of ovary, normal appendix.

The diagnosis of fibroma was later changed to that of Brenner tumor and this was confirmed by R. Meyer.

CASE 3.—Mrs. G. P., a 45-year-old white female, gravida i, para none, entered the hospital Feb. 14, 1927, complaining of left lower abdominal pain, increased with catamenia and associated with a bearing-down sensation, for one year and of a small, tender lump in the left groin for six months. The menstrual flow had been irregular and heavy for five years. Examination revealed an enlarged external inguinal ring on the right, the uterus forward and an irregular, nontender mass behind the uterus. A dilatation and curettage, bilateral salpingo-oophorectomy and supravaginal hysterectomy were performed. The patient was in good health seven and one-half years later.

*Pathologic Report No. 14567, Gross:* The specimen consisted of a multiple fibroid uterus with tubes and ovaries attached, the fibroids measuring up to 10 by 6 by 5 cm. The right ovary was atrophic, the left ovary cystic and slightly enlarged. *Microscopic:* The myometrium was normal; the glands of the endometrium were hypertrophied. Both tubes showed thickening of the walls and villi with round cell infiltration. One ovary showed fibrosis and a number of gland inclusions; the other contained many cortical glands, some cystic. *Diagnosis:* Multiple fibromyoma with chronic salpingitis and oophoritis.

On re-examination later the gland inclusions were found to be nests of epithelial cells of a one-millimeter Brenner tumor. This diagnosis was confirmed by R. Meyer.

CASE 4.—Mrs. E. A. C., a 49-year-old white female, gravida iii, para ii, entered the hospital June 7, 1928, complaining of passage of fecal material through the vagina, a "falling out" sensation in the vagina and occasional increased menstrual flow. Twenty-one years before she had had a dilatation and curettage, a resection of the right ovary, a left inguinal herniorrhaphy and a fixation of the round ligaments. The pathologic diagnosis was cystic degeneration of the ovary. At this second entrance, pelvic examination revealed a rectovaginal fistula, cystocele, rectocele, and prolapse. A dilatation and curettage, amputation of the cervix, anterior colporrhaphy, appendectomy, bilateral salpingo-oophorectomy and supravaginal hysterectomy were done. She was in good health seven years later.

*Pathologic Report No. 16001, Gross:* The uterus and cervix were normal except for a 1 cm. fibroid on the anterior wall of the fundus. On sectioning the right ovary a solid nubbin 1.5 cm. in diameter was found in the center. The left ovary contained a 2 cm. corpus luteum cyst. *Microscopic:* The myometrium and endometrium were normal. The fibroid showed hyaline change. The right ovary contained a small amount of normal stroma surrounding a mass of bundles of fibrous tissue, scattered between which were areas of epithelioid proliferation. Some of these areas contained lumens. There was no evidence of invasion or metastases. *Diagnosis:* Fibromyoma with hyaline degeneration, atypical carcinoma of the ovary (right) and discrete adenomyoma of the posterior surface of the fundus.

TABLE I. CONDENSED DATA CONCERNING TEN CASES OF BRENNER TUMOR OF THE OVARY

PATIENT HOSPITAL NO. PATHOLOGY NO.	AGE	GRAVIDA	PARA	YEAR	PREOPERATIVE DIAGNOSIS	SIZE OF BRENNER TUMOR	ASSOCIATED PATHOLOGY	ORIGINAL DIAGNOSIS	FOLLOW-UP
1. Mrs. L. Private case 2468	?	?	?	1910	Ovarian cyst	3 mm. in wall of ovarian cyst	Pseudomucinous cystadenoma 18 by 17 by 6 cm.	Missed	?
2. Mrs. C. S. 2859 7007	41	1	1	1917	Prolapse	2 cm. nodule, left ovary	Calcification of left ovary	Fibroma of ovary	Well 11 yr. P.O.
3. Mrs. G. P. 4475 14567	45	1	0	1927	Pelvic inflam.; rt. inguinal hernia	Microscopic	Fibroids; inflammation; many cortical glands, some cystic, in other ovary	Gland inclu- sions	Well 7½ yr. P.O.
4. Mrs. E. A. C. 46-210 16001	49	3	2	1928	Prolapse; recto- vag. fistula	1.5 cm. inside right ovary	Fibroids; discrete adeno- myoma; fistula-in-ano	Atypical carcinoma	Well 7 yr. P.O.
5. Mrs. E. J. W. Private 1992 15362	66	5	4	1927	Ovarian cyst	10 by 6 by 8 cm., left ovary	Endometrial and cervical polyps; diffuse adenomyoma; pseudomucinous cystadenoma, 20 by 17 by 13 cm., rt. ovary	Fibrosarcoma with epithelial inclusions	Well 3 yr. P.O.
6. Mrs. A. L. C. 20940 19093	68	5	4	1931	Procidencia with ulceration	0.5 cm., left ovary	Endometrial polyp; squamous cell carcinoma of vagina	Early carcinoma	Died 3 yr. P.O.—cir- culatory death
7. Mrs. L. L. 22818 21013	39	6	5	1932	Comp. lac. of perineum; fibroids	7 by 5 by 5 cm., right ovary	Fibroids; diffuse adenomyoma; inflammation	Granulosa cell tumor	Well 3½ yr. P.O.
8. Mrs. M. L. R. 26485 25495	44	1	2	1935	Ovarian cyst	Microscopic, left ovary, with early pap. serous cystadenoma	Multilocular pseudomucinous cystadenoma, 18 cm., right ovary	Brenner tumor	Well 1 yr. P.O.
9. Mrs. A. L. W. 28867 28925	37	1	0	1937	Fibroids	Microscopic	Fibroids; inflammation	Brenner tumor	Well 6 mo. P.O.
10. Mrs. E. C. S. 29229 29373	51	3	2	1938	Ovarian cyst	Microscopic, right ovary	Fibroids; papillary serous cyst- adenoma, left ovary	Brenner tumor	Well 3 mo. P.O.

lower abdominal pain for one year and increased menstrual flow for two months. Examination revealed a complete laceration of the perineum, a lacerated cervix, and a mass on the right side attached to the uterus. Dilatation and curettage, biopsy and cauterization of the cervix, bilateral salpingo-oophorectomy and supravaginal hysterectomy were effected. The patient was in good health three and one-half years later.

*Pathologic Report No. 21013, Gross:* The curettings were hyperplastic. The tubes were normal. The uterus had a 2 cm. fibroid in the fundus. The left ovary measured 3.5 cm. and contained a follicle cyst. The right ovary measured 7 by 5 by 5 cm. and was firm and fibrous throughout. *Microscopic:* Sections of the cervix showed chronic inflammation. The fibroid showed no malignant changes; the tubes and left ovary were normal. The right ovary consisted of bundles of fibrous tissue showing hyaline changes and scattered, irregular, small masses of epithelial cells with occasional central necrosis. The stroma of the endometrium was dense; the glands were hyperplastic and a few were dilated. There were a few endometrial glands within the myometrium. *Diagnosis:* Endometrial dysplasia; diffuse adenomyoma of the uterine wall; chronic cervicitis; fibromyoma; granulosa cell tumor of the right ovary; bilateral perisalpingitis.

A diagnosis of Brenner tumor was made later and confirmed by R. Meyer.

CASE 8.—Mrs. M. L. R., a 44-year-old white female, gravida i, para ii (twins), entered the hospital Dec. 12, 1935, complaining of abdominal swelling for eight months and of occasional urinary incontinence for many years. The menses had been normal until the menopause six years before entrance and there had been no bleeding since. Abdominal and pelvic examination revealed a cystic tumor filling the lower abdomen; the uterus was of normal size and mobility. Dilatation and curettage, cauterization of the cervix, supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed. She was well one year later.

*Pathologic Report No. 25495, Gross:* The specimen consisted of a multilocular cyst 18 cm. in diameter containing clear, stringy, mucoid fluid and of an atrophic uterus. The left ovary was fibrosed and atrophic. *Microscopic:* The myometrium and endometrium were atrophied. The cyst of the right ovary was lined with tall, columnar epithelium secreting mucus. On the surface of the left ovary were several areas of beginning papillary growth covered with flat to cuboidal epithelium; from these areas epithelial-lined crypts dipped down into the ovarian stroma. In the cortex of this ovary were a number of well-circumscribed islands of epithelial cells, several of which contained a central vacuole. *Diagnosis:* Atrophy of tubes, myometrium and endometrium; multilocular pseudomucinous cystadenoma, right ovary; beginning papillary serous cystadenoma and Brenner tumor of left ovary.

CASE 9.—Mrs. A. L. W., a 37-year-old negress, gravida i, para none, entered the hospital Nov. 1, 1937, complaining of a gradual enlargement of the abdomen for one year and of abdominal pain for one week before menses for three months. Menses had been regular but more profuse during the past year. The Wassermann reaction was positive. Abdominal and pelvic examination revealed an irregular, nodular tumor arising in the pelvis and extending to the epigastrium. Lysis of omental adhesions, supravaginal hysterectomy, bilateral salpingo-oophorectomy and appendectomy were done. The patient was well six months after operation.

*Pathologic Report No. 28825, Gross:* The uterus was enlarged and nodular, measuring 15 by 14 by 14 cm., and had one pedunculated fibroid measuring 27 by 19 by 19 cm. The tubes and ovaries were normal. *Microscopic:* In one ovary was an area consisting of dense fibrous stroma with numerous small masses of epithelial cells which were well differentiated and showed no evidence of malignancy. *Diagnosis:* Normal endometrium; submucous and pedunculated leiomyomas; normal ovary; Brenner tumor of ovary.

CASE 10.—Mrs. E. C. S., a 51-year-old white female, gravida iii, para ii, entered the hospital Feb. 12, 1938, complaining of a gradually enlarging abdomen associated with lumbar backache for three years. Menses had been regular until the menopause five years previously and there had been no bleeding since. A dilata-

The diagnosis of atypical carcinoma was later changed to that of Brenner tumor, and this was confirmed by R. Meyer.

CASE 5.—Mrs. E. J. W., a 66-year-old white female, gravida v, para iv, entered the hospital on Nov. 21, 1927, complaining of slight bleeding for one week. The menopause had occurred sixteen years previously and there had been no bleeding until the present illness. Pelvic examination revealed an irregular, nodular, cystic mass reaching to the umbilicus, a rectocele, cystocele, and laceration of the cervix. A dilatation and curettage, cauterization of the cervix, bilateral salpingo-oophorectomy and supravaginal hysterectomy were performed. The patient was in good health three years later.

*Pathologic Report No. 15362, Gross:* The specimen consisted of a multilocular, bluish-white, right ovarian cyst, 20 by 17 by 13 cm., containing slimy, yellow fluid. In one region the wall was thickened and indurated and on section had the appearance of beginning malignancy. There was a cervical polyp 2 by 1 by 1 cm. On opening the normal-sized uterus, a mucous polyp 5 by 3 by 3 cm. was found. The left ovary was solid, white and nodular, measuring 10 by 6 by 8 cm.; on section, several 1 to 2 cm. cystic areas were found. *Microscopic:* The cervical and endometrial polyps showed no malignant changes. The myometrium contained a few glandular areas. The ovarian cyst showed tall, columnar epithelium lining cavities. The stroma of the left ovary was dense and fibrous, containing peculiar cellular areas with occasional central necrosis. Neither mitoses nor invasion was found but the appearance was that of sarcomatous degeneration. *Diagnosis:* Atrophic endometrium with adenomyosis of uterine wall, endometrial polyp, cervical polyp, pseudo-mucinous cystadenoma of right ovary and fibrosarcoma with epithelial inclusions and necrosis of left ovary.

This diagnosis was later changed to Brenner tumor and confirmed by R. Meyer.

CASE 6.—Mrs. A. L. C., a 68-year-old white female, gravida v, para iv, was admitted on June 1, 1931, complaining of a protrusion from the vagina for one year and of slight staining from an ulceration of the protrusion for five weeks. Twelve years prior to this second admission she had had a repair of an umbilical hernia, a multiple myomectomy, and a fixation of the round ligaments with successful result. The menopause had taken place fourteen years before and there had been no bleeding until the present illness. Pelvic examination revealed a procidentia with an ulcerated, thickened area of the vagina near the cervix. An anterior colporrhaphy, excision of ulcer, and application of radium were performed. One month later, amputation of the cervix, excision of the ulcerated area, bilateral salpingo-oophorectomy, and supravaginal hysterectomy were carried out. The patient was in a good condition when seen two years postoperatively but died of circulatory failure three years postoperatively.

*Pathologic Report No. 19093, Gross:* The cervix was without visible evidence of malignancy. A 5 by 4 cm. portion of vaginal mucous membrane had a hard, ulcerated crater in the center. Both tubes and the left ovary were normal. The uterus contained an endometrial polyp. The right ovary was enlarged to 6 cm. by several cysts which showed no papillary ingrowths. *Microscopic:* The myometrium was fibrotic and contained a small fibroid; the endometrium was atrophic. The squamous epithelium of the cervix was thickened and there was round cell infiltration. The ulcerated area of vaginal mucous membrane showed, first, a layer of radium slough, then chronic inflammation and then an area of scattered alveoli with strands of active squamous cell carcinoma. The left ovary was atrophic but contained a few areas of epithelial proliferation scattered in a dense stroma; neither mitosis nor infiltration was found in these areas. *Diagnosis:* Squamous carcinoma of the vagina; retention cysts of the right ovary; endometrial polyp; early carcinoma, left ovary.

The diagnosis of early carcinoma was later changed to Brenner tumor and confirmed by R. Meyer.

CASE 7.—Mrs. L. L., a 39-year-old white female, gravida vi, para v, entered the hospital on Nov. 7, 1932, complaining of fecal incontinence for five years, right



that the proper normal adult proportion of the body of the uterus to the cervix is as 2 to 1, and that the measurement of the true infantile uterus is as of 1 to 2. There are various other proportions, the most important of which is the juvenile with the cervix and body of equal length. Meaker introduced a hystrometer to measure and a formula to give a number or "index" as an expression of normal or abnormal development. If the cervix measures 3 cm. and the whole uterus from cervix to the top of the fundus 9 cm. then the proportions are proper, that is, 6 cm. or 2 for the body and 3 cm. or 1 for the cervix. He has set arbitrary limits for his index and anything above 0.75 indicates normality and anything below 0.60 represents definite hypoplasia. In dealing with amenorrhea, sterility, etc., knowledge of this "index" is of great importance. The formula is as follows:

$\frac{1}{2} \frac{(\text{uterus minus cervix})}{\text{cervix}}$  equals the index. Placing the above figures in the formula  $\frac{1}{2} \frac{(9-3)}{(3)}$  or  $\frac{1}{2} \frac{(6)}{(3)}$  or  $\frac{1}{2} (2) = 1$  the index for the normal. These figures represent the perfectly developed uterus. If the cervix should measure 4 cm. and the whole uterine cavity from cervix to fundus 8 cm., the formula would be as follows:

$\frac{1}{2} \frac{(8-4)}{(4)}$  and the result 0.5, which would be an indication of underdevelopment. If the cervix should be longer, let us say 4 cm., as it is in the infantile uterus the calculation  $\frac{1}{2} \frac{(6-4)}{(4)}$  would give 0.25, an indication of real underdevelopment. His instrument or hystrometer has been redesigned and is illustrated in Fig. 1, A and B. This instrument is an ordinary uterine sound measured off into centimeters. A finely coiled spring is used as part of the apparatus so that the sliding part can negotiate the curve of the sound. The instrument is introduced into the cervical canal and when obstruction is met (at the internal os) the measurement is read at the proximal end of the sliding portion. This is recorded as 3 cm. or 4 cm., or whatever it reads. Then without withdrawing the instrument, for the reading is easy, it is advanced into the uterine cavity until it reaches the top of the fundus when another reading is made, for instance 7 cm. or 8 cm. These two measurements which represent the length of the cervix and the length of the entire uterus are then incorporated into the formula and the index obtained. Usually it is only necessary to think of the proportions and an index of the proper or improper development is immediately suggested. For example, if the cervix measures 3 cm. and the uterine cavity 9 cm., it is obvious that the body measures 6 cm. and the cervix 3 cm. and that therefore the proportions are adult normal.

Before inserting the probe the vagina must be cleaned out and the cervix painted. Usually the cervix is caught with a uterine tenaculum to hold it steady as in doing a dilatation, but occasionally both an "index" and a biopsy may be obtained without a tenaculum, the instruments passing easily by the internal os and into the uterine cavity.

In the early days of the clinic the Burch punch (Pilling) was used to obtain biopsy specimens because it was felt that with this instrument a piece could be removed from any part of the cavity desired. Because of the expense of the apparatus and the difficulty in keeping it in perfect working order it was discarded. Later a suction curette was used but the necessity for another pair of hands to maintain the suction, and because of the occasional plugging of the instrument with dried blood, it was given up. It then occurred to me that it would be easy to cup the knob on the end of the hystrometer and to use it to obtain specimens at the same time the uterine index was being made. This was done and proved useful. However, on occasions it was found that the cup of the curette caught at the internal os while being removed and made the biopsy painful, so that a smaller curette (Fig. 1, C) was made. The cup of the small curette has a small hole bored in the top to let out any secretions (blood, etc.) that may get in. After the hystrometer has

tion and curettage, removal of cysts of one ovary and an appendectomy had been performed elsewhere fifteen years before; a cholecystectomy had been done eight years before. Dilatation and curettage, supravaginal hysterectomy, left salpingo-oophorectomy and right salpingo-oophorectomy were performed. Three months later the patient was in good health.

*Pathologic Report No. 29373, Gross:* The uterus measured 5 by 5 by 3 cm. and there was a 1 cm. pedunculated fibroid at the right cornu. The right ovary and both tubes were atrophic. The left ovary was replaced by a multilocular serous cyst 15 cm. in diameter, containing a few papillary projections. *Microscopic:* In the right ovary was a 4 mm. nodule at one pole consisting of fibrous tissue with small islands and strands of pavementlike epithelial tissue without evidence of malignancy. *Diagnosis:* Atrophic endometrium; leiomyoma; atrophic ovary with Brenner tumor, right; benign papillary serous cystadenoma, left ovary.

### SUMMARY

Ten cases of Brenner tumor of the ovary have been presented, the diagnosis of seven of which has been confirmed by R. Meyer. The clinical and pathologic findings have been summarized and briefly discussed.

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## ENDOMETRIAL BIOPSY AND THE UTERINE INDEX

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THIS report is a description of two instruments used in the Ovarian Dysfunction Clinic of the Massachusetts General Hospital to determine uterine development and to obtain endometrial biopsies.

During the past five years the Pathology Department of the Massachusetts General Hospital has examined 1,500 pieces of tissue removed from the endometrial cavity. These specimens are part of a study being carried out upon patients with amenorrhea, dysmenorrhea, sterility, and abnormal uterine bleeding. The value derived is great and later a detailed report will be presented of the pertinent facts obtained. It is essential in gynecologic endocrine studies to know whether or not a given piece of endometrium agrees with the day of the menstrual cycle and whether the patient has ovulated or not. In a report written in 1936, Sturgis and Meigs described the various stages of the endometrium, and this same scheme for "dating" has been followed since. Later studies have convinced the authors that much more material must be viewed before accurate dating can become a certainty. There are many specimens that do, but many specimens do not coincide with the date of the cycle. It is likely that the end organ (uterus and endometrium) is important and that this organ may not respond perfectly to its ovarian stimulation. There may be underdevelopment of the uterus so that its indicator (the endometrium) cannot respond as it should. It is obvious that a method of measuring the proportionate size of the uterus must be developed if endocrine studies are to be carried out in addition to a method of obtaining tissue from the endometrial cavity.

In his book *Human Sterility* (Williams and Wilkins Company, 1934), S. R. Meaker describes his method of obtaining a "uterine index." This index is an indicator of the proportionate development of the cervix and uterus. It has been long recognized

Occasionally in patients with amenorrhea or prolonged bleeding it is difficult to obtain tissue with the sharp curette. It is then necessary to use the Burch punch to really "bite" out a piece of uterine wall with its very thin layer of endometrium.

The methods described above for obtaining an endometrial biopsy and the uterine index have been in use in our clinic for five years, and after removing more than 1,500 specimens from the uterus without any disasters, we feel that it has proved to be satisfactory, simple, inexpensive, and safe. Although a few specimens have shown unmistakable evidence of early pregnancy, only one patient has miscarried, and this was a sterility patient who had had two weeks of dribbling and probably was about to miscarry spontaneously.

In studying patients with endocrine disorders and sterility, endometrial biopsy must be done and the uterine index found, but it is very important to emphasize that this method of biopsy cannot be used to exclude cancer of the body and endocervix. In a suspected case a real curettage of the whole uterine cavity should be carried out.

### CONCLUSIONS

1. A method is described for obtaining endometrial biopsies and for measuring the proportions of the uterine cervix and body.

2. The method has been in use in the Ovarian Dysfunction Clinic of the Massachusetts General Hospital for over five years, and in no patient has any serious difficulty or sequela occurred.

3. The use of these two methods of investigation are recommended in the study of endocrine and sterility problems, but the method will not replace careful curettage in patients with suspected tumors of the inside of the uterus.

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## ASYMPTOMATIC AXIAL ROTATION OF A FULL-TERM UTERUS THROUGH 180 DEGREES

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(From the St. Vincents Hospital)

THE full-term uterus is quite frequently dextrorotated; however, axial rotation through 180 degrees is exceedingly rare. The literature has recently been reviewed by Robinson and Du Vall,<sup>1</sup> Feinor and Kaldor,<sup>2</sup> and H. F. Day.<sup>3</sup> Adding my case to the list makes a total of 36 such cases reported. Of these, 29 cases had associated pathology or uterine anomalies that may account for their rotation, and in 7 cases, including mine, no apparent reason for the rotation could be noted. The case I am reporting is the only one, so far as I have been able to determine, which was entirely asymptomatic.

Mrs. W., aged 31, gravida i, para 0, was first seen on Dec. 21, 1937, stating that her last menstrual period began October 29, 1937. Her past history revealed that she had had an appendectomy and removal of the gall bladder in 1924, a suspension of the right kidney in 1925, and a dilatation and curettage with radium implantation for menorrhagia in 1926. Her menstrual periods began at 13 years of age, interval twenty-six days, duration four days, with slight dysmenorrhea.

Physical examination revealed a young woman, of fair complexion, height 5 feet 3 inches, weight 122. Head and neck negative, heart and lungs clear, high right rectus scar, well healed, with no tenderness, also a scar over the right kidney region. Pelvic examination showed the outlet marital, glands negative, support adequate, cervix posterior, uterus anterior, size of a six weeks' pregnancy and freely movable, no palpable adnexal masses, the diagonal conjugate was not reached, all bony pelvis

been passed it is easy to insert the curette because its cup is smaller than the knob on the end of the sound. Thus after the sound has been passed, the direction of the canal is obvious and the curette follows easily. It is frequently unnecessary to use a tenaculum, thus relieving the patient of a somewhat uncomfortable sensation when the cervix is caught.

It is almost impossible to insert this curette into the uterine cavity and withdraw it without obtaining a perfectly adequate specimen from the endometrium. Its method of use is illustrated in Fig. 1, *D*, showing the curette beyond the internal os and in the uterine cavity. A slight pressure is made on one side and then it is turned around, and a similar pressure made on the other side, assuring two pieces of tissue. We have rarely found that these two pieces of tissue vary microscopically and do not believe it is necessary to strip the endometrium with the idea that many

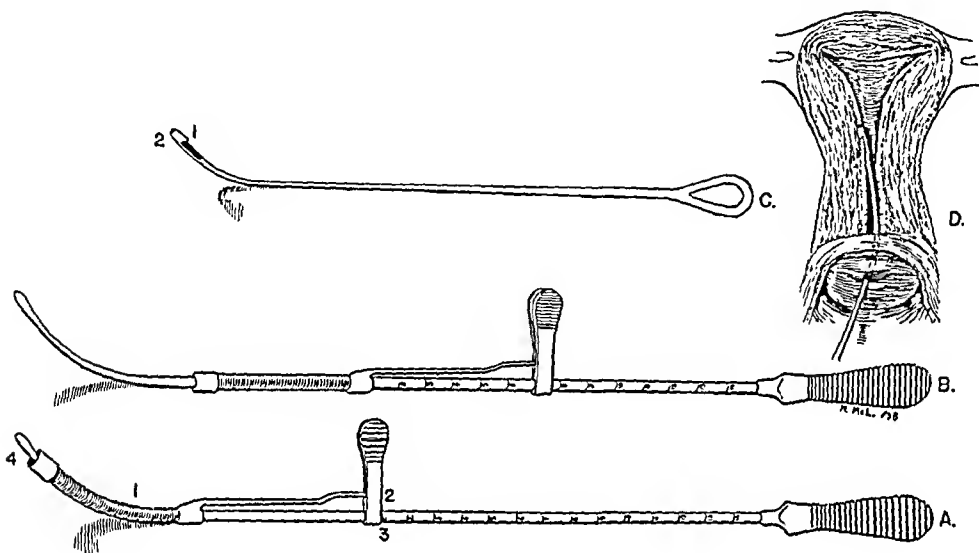


Fig. 1.—A, Hysterometer. 1. Coiled spring so that the curve of the sound may be passed; 2. spring clip which is used as a handle to move the measuring part of the apparatus and to hold it steady on the shaft; 3. area of measurement. Notice it registers 1 cm. and there is 1 cm. at 4. B. Showing the hysterometer measuring  $7\frac{1}{2}$  cm. as it would if the curved part were in the uterine cavity. C. Small steel cupped curette. 1. Sharp overhang to curette; 2. small hole in cup to allow escape of secretions. D. Curette removing tissue from the endometrium. The curette can be used numerous times to obtain tissue from different regions but a piece from either side is usually sufficient. These instruments are made by Codman and Shurtleff, Boston, Mass.

different types of endometrium may be found. It is well known that the endometrium just above the internal os is different and that it is not as responsive to hormones as the upper part of the endometrium, but if the curette is placed high in the cavity, good specimens of active endometrium are easily obtained. The specimens are removed from the cup of the curette with fine splinter forceps and are placed in Zenker's solution immediately. They are then cut in paraffin and stained with hematoxylin and eosin. Zenker preserved tissue gives better detail than formalin preserved tissue.

The trauma associated with passing the hysterometer, the curette, and the biopsy itself causes a moderate amount of pain similar to a uterine cramp. After a few minutes it passes away and the patient leaves the clinic without discomfort. The patient should be told that a dribble of blood may follow the biopsy for from two to four days and that this should not be misconstrued as a period. The patient on leaving is given a return postal card upon which to indicate the date of onset of her period following the biopsy. It has been noticed occasionally that if the biopsy is done near the time of an expected menstruation, the flow may be started and a true catamenia ensues.

findings were well within the range of normal. Joints and extremities normal, all reflexes active. Laboratory findings: Wassermann negative, hemoglobin 73 per cent, R.B.C. 4,910,000, urine negative for albumin and sugar.

Patient was seen at two-week intervals during the remainder of her pregnancy, during which time all findings were well within the range of normal. On July 5, 1938, a diagnosis of a transverse presentation was made. This was subsequently confirmed by an x-ray on July 26, 1938. Patient was subsequently seen at weekly intervals, and an elective cesarean section was decided upon for Aug. 7, 1938, which was approximately full term. Patient went into labor spontaneously on Aug. 5, 1938, at 10:00 A.M., was admitted to St. Vincents Hospital immediately. At the time of admission patient was having weak uterine contractions, and two hours later was operated upon under spinal anesthesia.

A low midline incision was made in order to enter the lower uterine segment. Upon opening the peritoneal cavity it was found that the uterus was rotated to the right 180 degrees, such that its posterior surface was presenting at the wound. The left round ligament was stretched diagonally across the uterus and measured about 2 cm. in diameter. The left broad ligament with tube and ovary was lying as shown in Fig. 1. Rather than attempt to deliver the fetus through a posterior incision it was decided to explore the upper abdomen, so the abdominal incision was lengthened to slightly above the umbilicus, thus enabling the hand to be introduced well over the fundus. The abdomen was entirely free of adhesions and the uterus seemed mobile such that with my hand up over the fundus I was able to rotate the uterus back to its normal position. A low classical operation was then done; a five-pound, nine-ounce fetus lying as a transverse presentation was found. A breech extraction was done on the fetus and the placenta and membranes extracted manually. A gauze pack was then put in the uterus with a shuttle through the cervix. The uterine wound was then closed in the usual manner. The uterus was then drawn up out of the abdomen and a thorough inspection made with no gross pathology or abnormalities noted. Abdomen was closed in the usual manner.

Her postoperative convalescence was uneventful. Mother and baby were discharged in good condition on the fourteenth postoperative day.

Follow-up examination on Sept. 6, 1938, showed the patient in good general condition, the uterus involuted, anterior, and freely movable, no palpable adnexal masses. Her subsequent course to date has been uneventful.

#### DISCUSSION

In deciding upon an elective cesarean in this case it was felt that the transverse presentation of the fetus was caused by stenosis of the lower uterine segment, due probably to the use of radium for menorrhagia ten years previous. However, no evidence of stenosis could be found at operation. Whether the transverse presentation caused a rotation of the uterus or vice versa I am unable to state. Certainly this patient did not complain of pain such as might accompany a rotation of this type.

A case of this type raises one other very pertinent question, that is, the advisability of attempting a manual correction of transverse presentation. If this is attempted, the procedure should be cautious and gentle, with no undue force, and certainly the patient should not have anesthesia during the attempted conversion.

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Fig. 1.—A drawing reconstructed from x-ray and surgery, illustrating a rotation of the uterus  $180^{\circ}$  to the right, with the fetus in transverse presentation.

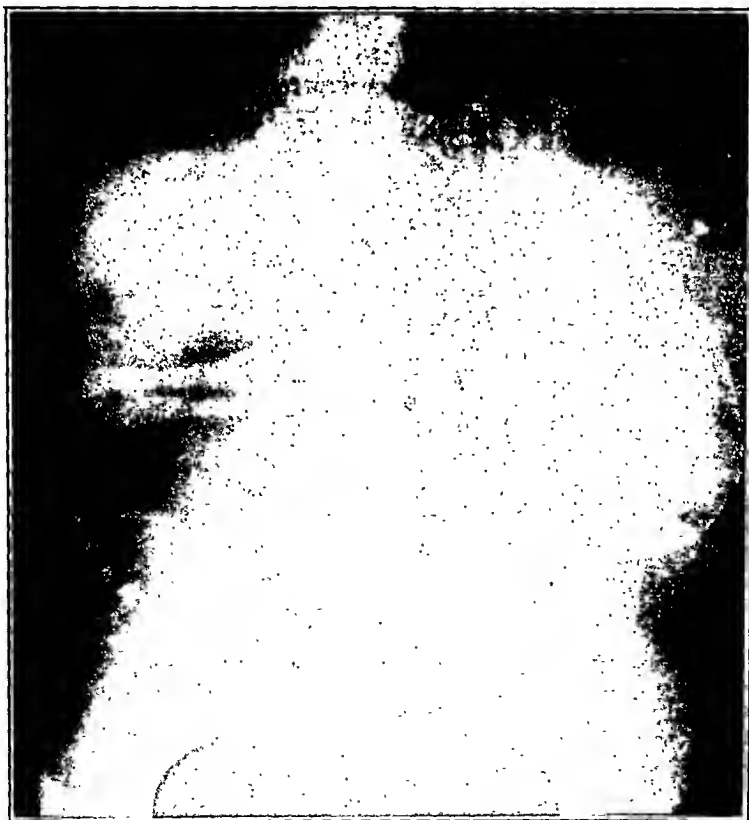


Fig 2.—Photograph of x-ray taken July 26, 1938.

sisted of highly vascular mesenchyme and had the form of cerebral hemispheres with prominent olfactory lobes and a cerebellum with two lobes. At the nape of the neck there was a flocculent mass protruding from a large opening which led downward into the spinal canal. They considered this mass to be broken down spinal cord. It was lost in preparation and was not sectioned. There was a wrinkled sheet of tissue loosely attached to the top of the head. They described this as typical of primitive nervous tissue having the characteristic appearance of the primitive neural tube with ependymal, mantle and marginal layers. Their conclusions were that the condition arose by failure of the neural tube to form from the neural plate in the cranial region at about the fourth week.

Attention is drawn to the flocculent mass described above by Dodds and DeAngelis. In its site it resembles the angiomatous mass seen in the specimen illustrated here.

Although no sections of the 10 mm. embryo have been made, the gross appearance of the mass at the nape of the neck is such as to leave little doubt that it consists of blood-filled tissue. Similar conditions are commonly seen in older specimens of anencephaly. It would seem only reasonable to assume that in this embryo the anencephaly resulted from an angiomatous growth in the tela chorioidea of the fourth ventricle. This results in a diminished blood supply to the brain and consequent atrophy. The condition must occur after the fourth week, because there is no apparent defect of the eyes. Against this postulation is the fact that new growths have never been demonstrated in fetuses. Mall's collection of embryos has been studied with care and two or three were seen to be somewhat similar to the one described here but no detailed account of their structure is given in his paper since he was concerned with the pathology of the membranes.

The reasons for not sectioning this embryo are: (1) The condition of the tissue is indefinite, the embryo may have been dead for some time before it was fixed, (2) it makes a valuable museum specimen as it is and sectioning may result in nothing.

#### SUMMARY

1. An embryo 10 mm. long is described in detail and its age is estimated to be 6.5 weeks.
2. It shows definite anencephaly and is characterized by what appears to be an angiomatous mass at the occipital region.
3. Anencephaly is, in this case, probably caused by an angiomatous growth originating in the tela chorioidea of the fourth ventricle.
4. This specimen is one of a very small number in which anencephaly has been noted in an embryo.

I wish to express my thanks to Professor D. C. Matheson for his assistance.

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# ANENCEPHALY IN A HUMAN EMBRYO TEN MILLIMETERS LONG

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THE embryo described here was obtained as the result of a spontaneous abortion from an unmarried woman 26 years old. She gave no history of amenorrhea and the possibility of pregnancy was denied. It was determined later that the father was about 65 years of age. The ovum was unruptured and measured 6 cm. in diameter. On opening the sac it was found to be filled with dark, greenish-colored amniotic fluid that had the consistency of bile. The quantity of fluid was excessive for the stage of development of the embryo. Since the clinical history of the patient was of no value in determining the age of the embryo, its size and developmental characteristics were used to estimate its approximate age.

On careful examination the embryo was found to be anencephalous. Its crown-rump length was 10 mm. What appeared to be an angiomatous mass was seen to extend from the occiput to the lumbar region. This mass covered a complete spina bifida. Anterior to the mass was a lighter colored structure which appeared to be part of the brain. This consisted of two anterior lobes and a triangular posterior part. These were probably atrophic cerebral hemispheres and midbrain, respectively. The left lobe was seen to be perforated when re-examined some months after first obtaining the specimen. The angiomatous-like mass appeared to be very fragile and a small portion had fallen away. The head was acutely dorsiflexed upon the shoulders, typical iniencephaly. The mouth was open and the tongue protruding. The eyes were situated well forward on the head. The nasal pits were discernible with the naked eye. On viewing the embryo anteriorly the parts referred to above as portions of the brain were seen to be flattened out. They extended downward in an overhanging manner and partially covered the frontal region. Laterally, these parts joined the so-called angiomatous mass where one might expect to find the developing ears. There was no evidence of these structures. The spine showed no convexity and no tail could be seen. The abdomen was prominent as in a normal embryo at this stage. There was no evidence of an umbilical hernia and the gut appeared to be within the abdomen.

The gross appearance of the sac was normal except for its size. It was comparatively large due to excessive amniotic fluid. Chorionic villi were present over the whole ovum. There appeared to be old blood clot adherent to the amnion.

Examination of the embryo under a dissecting microscope ( $\times 10$ ) showed that the nasal pits had probably been formed recently. They were quite shallow. Facial fissures could not be defined with certainty, but there was a slight indication of a groove between the fused globular and maxillary processes. The only evidence of the developing ears was a pit on the right side just posterior to the mandibular arch. There were no tubercles seen and the hyoid arch was not defined. The branchial grooves could not be seen. The three segments of the forelimb could be recognized easily. The rudiments of the fingers were seen as very shallow indentations at the margins of the hands. The hindlimb also showed division into its main parts but the rudiments of the toes were not visible.

The absence of facial fissures and the presence of rudimentary fingers would suggest that the embryo was at the seven-weeks' stage of development. The absence of rudimentary toes and of an umbilical hernia indicate an earlier stage and its age was therefore estimated to be about 6.5 weeks.

The available literature on anencephaly and related malformations contains only one recent report of such a condition in an embryo, that of Dodds and DeAngelis (1937). They described an embryo of seven weeks and crown-rump measurement of 16.5 mm. which had a deformity of the head with complete absence of the brain. The upper portion of the head had a formation simulating a brain. This con-



Below this was a band extending to the mass in the front of the segment of the uterus. The left fornix was negative. Charcoal fed to the patient at this time appeared in the vagina the following morning.

On April 10 x-ray examination revealed a large shadow in the pelvis, which was stated to be a distended bladder rather than a fetal skull. Smaller shadows to the right of the fifth lumbar vertebra were suggestive of fetal bones.

The patient's pulse and temperature were normal on admission, Hb. 70 per cent; R. B. C. 4,320,000; W. B. C. 12,000; polymorphonuclears 74 per cent. Sedimentation time seventy minutes to the 18 mm. line. The urine and Wassermann reactions were negative.

At the time of operation the uterus was normal in size, drawn over to the right side of the pelvis, where it was fixed in position by a chronically inflamed tube and an inflammatory cyst attached to the side wall of the pelvis and extending in front of the uterus. There was a large mass in the right side, lower part of the abdomen, made up of adherent loops of small intestine and sigmoid and the remnants of a decomposed fetus. The skull bones which formed the upper limit of the mass had eroded into the lumen of the small intestine for a distance of about three inches, giving rise to an enterouterine fistula which opened into the posterior superior aspect of the fundus uteri. On separation of the adherent loops of small intestines and sigmoid, there was also found an opening into the large intestine 1 inch in diameter. The decomposed fetus consisted of skull bones, brain, part of the chest, and a few long bones. The left tube and ovary were normal in appearance.

After exploring the pelvis the mass in the lower part of the right side of the abdomen was opened, and the decomposed fetus was removed. Supravaginal hysterectomy and right salpingo-oophorectomy were done, with removal of a cyst on right side. The adherent loops of intestine were separated, 8 inches of ileum was resected and an end-to-end anastomosis done. The opening in the sigmoid was closed. Raw surfaces were peritonized. The wound was closed in layers, with drainage.

Her convalescence was not uneventful. There was a moderate amount of shock following the operation. On the third day she had a rather severe reaction following the injection of glucose. On the sixth day the wound showed evidence of infection. In a little over two weeks the infection was pretty well cleared up and she was doing nicely. A week later she was operated upon for an acute obstruction of the small intestine on the left side of the pelvis at about the junction of the distal portion of the jejunum with the ileum by a broad area of dense adhesions, apparently at the site of the previous fistulous opening in the sigmoid. The site of the anastomosis in the small intestine showed no evidence of obstruction. The obstruction was relieved and the patient returned to bed in good condition. Her subsequent course was uneventful and she is in excellent condition today.

#### PATHOLOGIC FINDING (DR. I. G. GERBER)

One specimen consisted of a uterus, and right adnexa. The uterus was amputated supraeervically and measured 5.0 cm. long. It was 5.0 cm. wide at the fundus and 3.5 cm. thick. The serous surface was covered with fibrous tags on all aspects. The left adnexa had been resected close to the tubal angle. On the right lateral border, just 1.0 cm. below the isthmus of the tube, there was an opening in the uterus, about 1.5 cm. in diameter. This could be probed directly into the endometrial cavity. The endometrial cavity was 4.0 cm. long and 3.0 cm. wide at the fundus. The myometrium was 1.6 cm. thick, and on section showed many scattered, small, pinhead-sized hemorrhagic foci. The endometrium was prominent, granular, and hemorrhagic with scattered superficial areas of grayish green appearance. The opening in the lateral uterine wall was covered by a similar gray green exudate, which extended about the orifice and onto the broad ligament and over the mesosalpinx, and along the mesial pole of the ovary. The tubo-ovarian ligament was shortened and thickened, and showed hemorrhagic discoloration. The ovary was 4.0 cm. in diameter, and cystic to the feel. On section it presented a large corpus luteum and adjacent to it several pea-sized, thin-walled cysts containing hemorrhagic thin fluid. The ovarian tissue was edematous. The tube was 11.5 cm. long and 1.2 cm. in average diameter. Its serosal surface was covered by fibrous tags.

## ENTEROUTERINE FISTULAS

WILLIAM A. DWYER, M.D., PATERSON, N. J.

IN 1933 Danforth and Case<sup>3</sup> reviewed the recorded history of enterouterine fistulas and found 58 authentic cases. Kirchners reported a case of sigmoidouterine fistulas. Since then, including cases not previously noted, 12 additional cases have been reported.

The following case of enterouterine fistula presents several interesting points. First, thirteen months after the onset of pregnancy, the fetus was finally extracted. Second, one cannot say with any degree of assurance that this was a traumatic rupture of the uterus following an attempt to empty the uterus, for there is a very strong possibility of its being a spontaneous rupture with a partial escape of the fetus into the abdominal cavity. This much we do know: the injury to the intestine was not instrumental but was caused by the skull bones perforating their way into the lumen of the gut.

The history of this case is that the patient became nauseated and was seized with excruciating pain in the epigastrium two hours after eating. The pain was so severe that the patient was unable to move. Her face was pale and her body covered with a cold sweat. At the time she was six months pregnant. The fundus uteri was at the level of the umbilicus. The cervix was closed. Her pregnancy up to this time was uneventful except for a complaint of right lower quadrant pain at two months. She had had her last regular monthly period on March 17, 1936 and had felt life just before the fifth month. With the onset of pain, however, fetal movement disappeared. For three days she complained of cramps in the hypogastrium and some vaginal bleeding. The external os, however, was closed, the cervix was soft and the fundus just below the umbilicus. The patient remained in bed three months. During this interval there was a constant brownish, foul-smelling vaginal discharge. Examination at the end of this period showed a fetal leg protruding through the cervix. Three days later the leg dropped out of the vagina. The following week there was occasional lower abdominal pain with a brownish vaginal discharge and several small fetal bones were expelled. The abdomen was soft and the fundus just below the level of the umbilicus. A month later (November 20) the discharge was less. The patient looked well, was out of bed. Her temperature and pulse were normal. The fundus was below the umbilicus, small and firm. The cervix was small, high up in the vaginal vault, closed. For the next two months she continued to pass bones per vaginam. Toward the end of that time, though the abdomen was soft, there was slight tenderness in the iliac fossae with a sense of a tender mass in the right lower quadrant.

On January 26, 1937 under a general anesthetic the cervix was dilated and 15 bones, including ribs and arm bones, were extracted. She was well for three weeks. Then she began to complain of pain in the left lower quadrant. This was followed by diarrhea lasting five days, toward the end of which she noticed bits of carrots and tomato skin in the vaginal discharge.

On April 9, 1937 the patient was admitted to the Gynecological Ward at St. Joseph's Hospital, complaining of foul-smelling vaginal discharge with a decided fecal odor and appearance, containing at times undigested food remnants and fetal bones. The vulva and labia were irritated.

Vaginal examination at the time showed the cervix high up in the right side of the vault, small and almost flush with the vault. It could not be brought down. The external os was open about  $\frac{1}{4}$  inch. Situated above the level of the internal os and apparently outside the uterus, anteriorly, was a small soft mass about 5 inches in diameter. The uterine cavity extended upward and to the right for a distance of six inches, and fetal bones could be distinctly felt with the sound. The fundus was fixed in position by an indurated mass that extended from the right side of the uterus to the right iliac fossa as far as the anterior superior spine.

*Note:* The presence of focal decidual reaction together with syncytial giant cells in the uterus speaks for a probably intrauterine pregnancy.

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99 PARK AVENUE

## SIGMOIDAL CUTANEOUS (FECAL) FISTULA

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THIS case is presented in view of the unusual type of accident caused by an abortionist, and because it demonstrates that iodized oil may be a valuable therapeutic agent in some types of large bowel fistula communicating with the skin.

Mrs. C. O. S., a 47-year-old, native white woman, was first seen June 17, 1937, at her home with complaints of lower abdominal and pelvic pain. The patient appeared subacutely ill. The history revealed similar attacks "many years ago," with the present illness extending back for some two weeks. There had been a discharge of mucopurulent character associated with the menses. The temperature was 101° F., pulse 96. The past history did not reveal any illnesses of importance. The family history was not relevant. There were two adult children, living and well. Both pregnancies had been normal and uneventful, and she denied ever having any uterine manipulation. The menses were regular, every twenty-eight to thirty days, lasting from four to five days, and of average flow. There was a moderate dysmenorrhea with some exacerbation recently. Abdominal examination disclosed marked tenderness throughout the entire lower abdomen, with diffuse muscle spasm. Vaginal examination revealed an extremely tender mass the size of a large orange in the left adnexal region. The sedimentation rate was rapid, falling 18 mm. in twelve minutes.

A diagnosis of an acute left tubo-ovarian abscess was made and treatment carried out at home. Subsequently, the sedimentation rate, which had been persistently rapid, gradually returned to within normal limits, and the mass became partially resorbed. Eight weeks after initial examination, the left sided mass was approximately one-half its original size and the sedimentation rate was consistently within normal limits. At this time operation was recommended and the patient was admitted to the hospital on Oct. 17, 1937. The red blood count was 4,130,000, the white count 12,050, and the hemoglobin 70 per cent (Dare). A blood Wassermann test was negative. The urinalysis revealed numerous pus cells, but was otherwise not significant.

At laparotomy a great number of adhesions were found, with the omentum plastered down to the bladder and the uterus, both anteriorly and posteriorly. Some loops of small bowel were adherent to the posterior aspect of the uterus. These adhesions were freed. There was a cordlike structure extending from the sigmoid at the rectosigmoid junction to the fundus of the uterus at its midpoint. This was cut upon in the belief that we were dealing with an unusually thick fibrous band. It was found to contain a rubber catheter with both ends cut upon a sharp bias,

The fimbriated extremity was patent and permitted ready probing along its entire length. The mucosa was pale gray and moist. Attached to the proximal aspect of the tube there was a flap of peritoneum measuring 4.0 by 4.0 cm.

A second specimen consisted of a number of fetal bones. These represented skull bones, and short and long bones of the extremities. The bones were covered by a dirty grayish exudate, and were soft. Some were granular and friable.

A third specimen consisted of a portion of small intestine, which was 18.0 cm. long. On its serosal aspect there were a number of fibrous tags. There was a central defect in the intestine which was 9.0 cm. long. At the site of the defect the edges were ragged, ulcerated and piled up. The ulceration was about 5.0 cm. wide and almost completely encircled the bowel lumen. There was a small amount of mesentery attached which was discolored and thickened. Upon opening the intestine the wall was found to be markedly thickened. The mucosa at the site of the defect was hemorrhagic and ulcerated. Proximal and distal to the ulcerated area the mucosa was intact, and somewhat edematous.

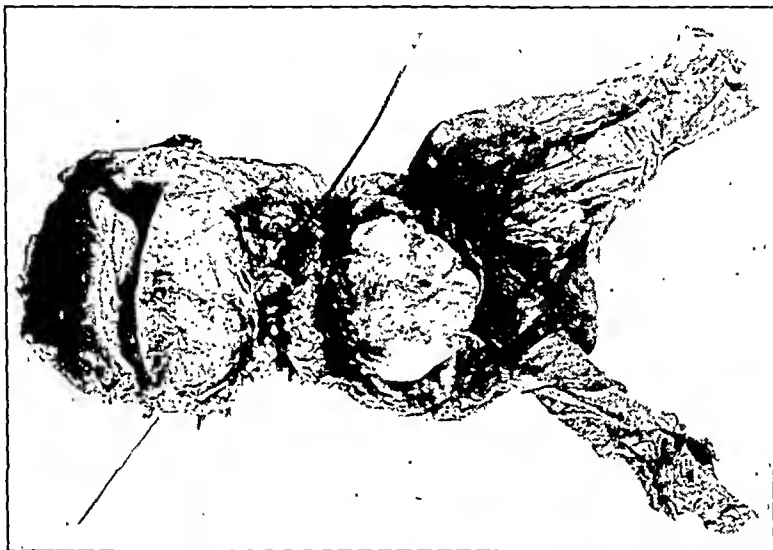


Fig. 1.—Uterus and right adnexa. Probe shows communication between endometrial cavity and abscess in broad ligament from which site remnants of fetus were removed.

*Microscopic Examination.*—The bones were not examined. Sections of the uterus showed a replacement of the endometrium by a broad layer of fibrin and inflammatory cells consisting chiefly of polymorphonuclear leucocytes and lymphocytes. The inflammatory reaction extended into the myometrium at several points. Where residual endometrial glands were present, these were small and collapsed and their surface covered by masses of fibrin. Other sections, taken near to site of perforation, showed areas of decidual reaction of the endometrium in which no glands were seen, and scattered areas in which there were syncytial giant cells. Chorionic villi were not noted. Sections of the tube and ovary showed chiefly adventitial inflammatory reaction with edema. Examination of the intestine revealed an extensive inflammatory reaction involving all coats, with marked edema and hemorrhage. There was complete necrosis of the mucosa with replacement fibrosis of the muscularis, and the serosa was covered by a layer of fibrin and polymorphonuclear leucocytes. There were scattered calcific foci in the subserosa with foreign body giant cell reaction and many pigmented macrophages.

*Diagnosis.*—Supracervically amputated uterus showing acute purulent endometritis and subacute myometritis, with decidual reaction and syncytial giant cells. Acute necrotizing enteritis. Perisalpingitis and peri-oophoritis. Corpus luteum and follicular cysts of the ovary. Perforation of the right lateral uterine wall, with localized abscess. Fetal bones.

and measuring 31 cm. in length. Approximately half of this rubber tube was found lying in the uterine cavity, piercing the fundal wall, and traversing the cordlike structure. The distal half of the tube was in the sigmoid directed toward the splenic flexure of the colon (Fig. 1). The catheter was removed and the sigmoidal and uterine openings were closed by fine catgut sutures. Two drains of soft rubber were inserted to the sutured sigmoid colon and brought out through the lower angle of the abdominal wound. The cordlike structure, through which the catheter traversed to the sigmoid, was removed and reported histologically as "a mass of chronic inflammatory fibrous tissue partially infiltrated by a subacute and acute inflammatory exudate of granulation tissue."

The soft rubber drainage tubes were totally removed by the fifth day after operation. The immediate postoperative course was uneventful and the patient was dismissed in two weeks. At this time there was a small amount of serosanguineous material at the drainage site. Approximately one month later the character of this discharge had become definitely fecal in appearance and odor (Fig. 2). Methylene blue injected into the abdominocutaneous opening appeared quickly at the anus. The amount was small but the drainage persisted for more than four months.

More than four months after operation the sigmoidal cutaneous fistula was still discharging despite all attempts at conservative treatment. The patient, therefore, was treated by means of the introduction of iodized poppy seed oil (lipiodol) into the fistulous tract (Mendelsohn and Schriver).<sup>1</sup> The intestinal contents were evacuated by means of small irrigations; a nonresidue or liquid diet was administered, and salines were used to help empty the entire gastroenteric tract.

Four to 10 c.c. of lipiodol were slowly injected into the tract through a small soft catheter which had been previously passed through the cutaneous opening and the tube then gently removed. A plug of gauze was then placed over the mouth of the opening. This was repeated at four- to five-day intervals, and at the end of approximately three weeks the tract had completely closed.

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**McCullagh, E. Perry, and Cuyler, W. Kenneth:** The Friedman Test and Pituitary Tumor, *Endocrinology* 21: 8, 1937.

Positive Friedman test results have been observed in 8 of 15 cases of pituitary tumor. The 7 cases in which negative Friedman test results were obtained are described briefly. The diagnosis of tumor was verified at operation or autopsy in 4 instances and histologic descriptions are available in 3; one was an acidophilic adenoma, one a basophilic adenoma, and the other a cystic adenoma which contained large numbers of both acidophilic and basophilic cells.

Of the 8 cases in which positive reactions were obtained, the presence of tumor was verified at operation or autopsy in 4 instances. Two were basophilic adenomas, one of which was found in a patient with the syndrome of pituitary basophilism; one was an acidophilic adenoma, and one a papillary carcinoma of Rathke's pouch involving the pituitary. Of the unverified tumors, 3 occurred in patients with acromegaly and therefore these tumors were probably acidophilic adenomas; a fourth was associated with signs of hypogonadism.

In cases of pituitary tumor in which the Friedman test reaction is positive, radiation therapy to the pituitary may be followed by marked diminution in the excretion of prolactin as judged by this test; in two instances, this has been accompanied by a diminution in the excretion of testicular hormone.

J. THORNWELL WITHERSPOON

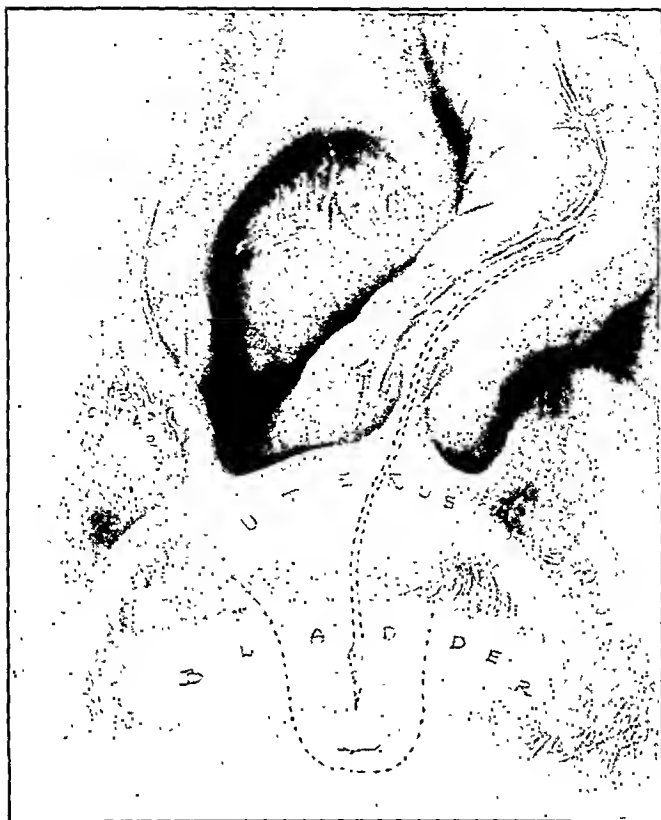


Fig. 1.—The catheter is seen piercing the posterior uterine wall and its distal portion lying within the sigmoid.

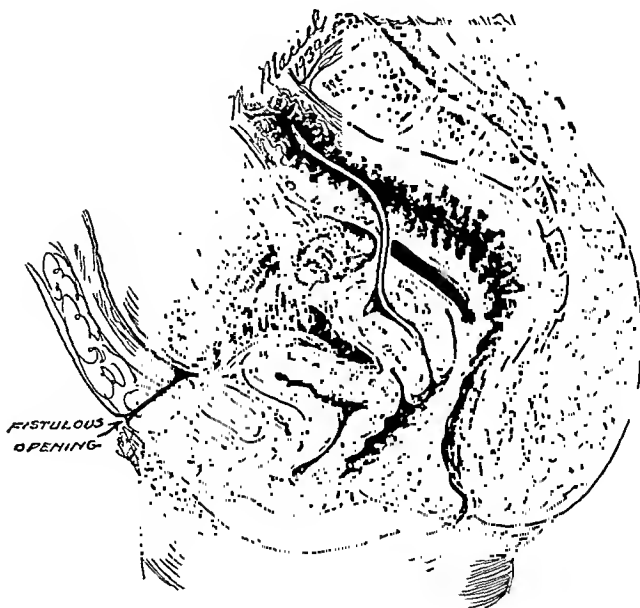


Fig. 2.—The fistulous opening is seen suprapubically. The catheter shown had been removed at operation.

facts presented might prove valuable in effecting a further reduction. This study included all deaths in which pregnancy or childbirth was mentioned by the physician who registered the death and also the deaths of women who were between the ages of 15 and 49 years and who were shown by birth certificates to have been delivered of a live or stillborn infant within three months prior to death. The registrar of the Bureau of Vital Statistics copied death certificates of all cases in which the puerperal state was mentioned and the physicians who signed these certificates were interviewed personally by physicians from the State Department of Health. All physicians were willing to cooperate and expressed approval of the survey as it was being made. This report will be presented elsewhere as the first of a series of annual reports by the Committee. The survey for 1938 is well under way.

The third and final objective of the Committee for 1938 was the launching of a program designed to reduce the incidence of neonatal mortality. According to the Director of the Division of Child Hygiene of the State Department of Health, approximately 30 to 40 per cent of the neonatal deaths in North Dakota are due to prematurity. The Committee has adopted the following plan:

1. The establishment of recognized methods of management and feeding of the premature infant.
2. The purchase and distribution of low cost incubators to North Dakota hospitals and the eventual placement of incubators in other key spots in the state where facilities are widely spaced.
3. The adoption of a modern, recognized technique of resuscitation of premature and newborn infants in all hospitals.
4. The establishment of a standard summary record form, such as that designed by Dr. R. G. Moe of Duluth, in all hospitals so that statistical data can readily be collected.
5. The carrying out of an educational program of seminars to be conducted by pediatricians selected by the Committee.
6. The securing of statistical data on the causes of neonatal deaths both in hospital and in home deliveries.
7. The publication of a preliminary report of this plan as information becomes available and as conditions warrant.

The Committee feels that these objectives have the support of the physicians. Without this support this or any other program looking toward a reduction of maternal and infant mortality would fail. The members of the Committee are private practitioners who know conditions in the rural and small urban communities in this state. Working with a State Health Department that knows the problems and has the viewpoint of the private practitioner of medicine, it hopes to make effective the all-important patient-private physician relationship, the backbone of medical practice in general and particularly in the fields of obstetrics and pediatrics.

# Department of Maternal Welfare

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CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

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## A REPORT ON THE PROGRAM OF THE NORTH DAKOTA COMMITTEE ON MATERNAL WELFARE AND CHILD HEALTH FOR 1938

JOHN H. MOORE, M.D., F.A.C.S., CHAIRMAN, GRAND FORKS, N. DAK.

THE North Dakota Committee on Maternal Welfare and Child Health has been occupied during 1938 with three major objectives in its plan to further maternal and child welfare throughout the state. At its final meeting for the year, held in Grand Forks, N. Dak., on Dec. 17, 1938, the entire personnel of the committee, consisting of Dr. J. F. Hanna and Dr. Ralph E. Pray of Fargo, Dr. J. L. Conrad, Jamestown, Dr. Paul W. Freise, Bismarck, Dr. E. M. Ransom, Minot, Dr. M. D. Westley, Cooperstown, Dr. John D. Graham, Devils Lake, Dr. Philip H. Woutat, Grand Forks, Dr. Maysil M. Williams of Bismarck, State Health Officer and Secretary of the Committee, and the Chairman, Dr. John H. Moore of Grand Forks, was in attendance.

The presence of Dr. August C. Orr and Dr. Elizabeth Smith of the Department of Maternal Welfare and Child Hygiene of the North Dakota State Department of Health was made possible by Dr. Maysil M. Williams who, in her dual role of State Health Officer and Secretary of the Committee, has continued the policy of cooperation with the Committee.

The first major objective for the year was a continuation of the Educational Program for Physicians. A subcommittee consisting of Dr. Ralph E. Pray and Dr. J. L. Conrad secured Dr. William F. Mengert, Associate Professor of Obstetrics and Gynecology at the University of Iowa, and Dr. W. H. Thompson, Assistant Professor of Pediatrics at the University of Minnesota, to give this year's course in Obstetrics and Pediatrics. Approximately 300 physicians attended the combined courses given in five cities during October, 1938. Late afternoon and evening sessions were held in each city visited for two successive weeks, a day in each city. That this plan was popular was evident by the replies to a questionnaire sent to the physicians upon the termination of the course. The majority favored continuing this plan another year and October was favored as the month in which to hold the courses. Many facts of interest were revealed by the questionnaire, and these will be used by the subcommittee in its plan for the courses in 1939.

At the conclusion of the course the booklet *Maternal Care*, approved by The American Committee on Maternal Welfare, Inc., was sent to physicians by the State Department of Health with the endorsement of the North Dakota Committee.

The Committee has authorized its subcommittee on the Educational Program for Physicians to enlarge its work for 1939, and it is hoped that more intensive postgraduate education will be made available to physicians thereby. It is certain that this type of instruction is very popular among North Dakota physicians.

The second major objective of the Committee for 1938 was an individual analysis of all maternal deaths occurring in North Dakota. The study was started for the year 1937 by the State Department of Health, Division of Child Hygiene, at the request of the North Dakota State Committee on Maternal Welfare and Child Health. While North Dakota has a low maternal mortality, it was felt that an individual analysis of all maternal deaths and a "break-down" of all the



# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### The Newborn Infant

Donaldson, S. W.: A Study of the Relation Between Birth Weight and Size of the Thymus Shadow in 2,000 Newborn, Ohio State M. J. 34: 538, 1938.

Of 2,000 newborn infants 18.4 per cent showed roentgenologically some degree of enlargement of the thymus, and 11.15 per cent were classified as definitely enlarged. The percentage of enlargement in the heavier babies is higher in the male. The heaviest baby in both groups was negative for thymic enlargement. The uniformity of the percentage of enlargement in the normal weight babies with a gradual increase as birth weight increases would imply that the size of the thymic shadow was proportionate to birth weight rather than that the gland was pathologically enlarged.

No ill effects were noted from small doses of radiation administered as a prophylactic measure. Not enough evidence was presented in this series to indicate that only those babies weighing more than 8½ pounds should be examined for an abnormal thymus shadow. Therapy was administered merely upon roentgen ray evidence of enlargement. Decrease in the size of the thymus shadow was noted in all patients treated and re-examined. No thymic death has occurred in any child in this study as far as the author's present records are concerned.

J. P. GREENHILL.

Kaern, T.: The Birth of Abnormally Large Children, Acta obst. et. gynec. Scandinav. 16: 189, 1936.

The author analyzed a series of 228 children who weighed more than 4,500 gm. at birth. In the Copenhagen clinic the incidence of these children was 0.9 per cent. Among the etiologic factors accounting for these large children the author mentions the sex of the child, the mother's age, her height and weight, and previous births. The incidence of operative intervention was 19.3 per cent. The shoulders gave particular difficulty during delivery. Hemorrhages of more than 500 c.c. occurred in 24.1 per cent of these cases in comparison with the usual incidence of 4.9 per cent in the author's clinic. The death rate among the large children was 14.9 per cent as against 3.2 per cent for all the newborn. The author believes that labor should be induced before term when children have reached a normal birth weight.

J. P. GREENHILL.

Holtz, S.: The Causes of Premature Labor and the Prognosis of Babies Born Before Term, Gynécologie 35: 65, 1936

In a series of over 60,000 labor cases the author found that 313 babies were born before term (5.1 per cent). Premature labors were not found to occur more frequently in primiparas than in multiparas. The age of the mother was not a factor. However, abnormal presentation such as breech occurs much more frequently among premature babies than among those at full term. Thirty-nine of the babies died before term and 18 died during labor. Most of the children were born alive and subsequently died of debility. The author comes to the conclusion that the prognosis of babies born before term is very bad. Of the babies weighing less than 2,000 gm. 21 per cent died before labor, 8 per cent during

# Society Transactions

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## CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF DECEMBER 16, 1938

The following papers and case reports were presented:

**Case of Krukenberg Tumor.** Dr. W. C. Danforth.

**A Case of Spontaneous Abortion Through Posterior Wall of the Cervix.** Dr. M. J. Kiley.

**A Preliminary Report on the Use of Sulfanilamide in Puerperal and Post-abortual Infections.** Dr. T. J. Morris. (For original article, see page 67.)

**Use of a Sulfanilamide Derivative in the Treatment of Gonorrhea in Pregnant and Nonpregnant Women.** Drs. E. J. Bomze, P. G. Fuerstner and F. H. Falls. (For original article, see page 73.)

**The Excretion of Free and Acetylsulfanilamide in Human Breast Milk.** Drs. L. R. Hac, F. L. Adair and H. C. Hesseltine. (For original article, see page 57.)

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**Salatich, P. B.: Varicose Veins of the Broad Ligament and Their Consequences,** South. M. J. 31: 697, 1938.

The failure of various operative procedures for the correction of uterine displacement to alleviate backache, menstrual disturbances and other associated symptoms suggested that possibly additional unrecognized factors might exist. From pre- and postoperative examinations it was observed that those women whose symptoms were most marked and persisted following round ligament shortening and suspension procedures had variable degrees of enlargement of the veins of the broad ligament.

The most distressing symptom associated with this condition is pain which characteristically is influenced by posture, being aggravated by standing. Various menstrual disturbances may occur, especially in younger patients; these develop upon a basis of ovarian congestion. A watery leucorrhea is common.

If, on pelvic examination there is no palpatory evidence of tubal or ovarian enlargement or pain, dilated veins should be considered as a possible etiologic factor. If they are present considerable pain will be caused by pressing upward in the parametrium with the fingers at the sides of the cervix in line with the axis of the uterus. Some softening of the cervix is noted, and the uterus though boggy need not be retroverted.

Conservative operation is recommended for the relief of the condition. The procedure includes vein ligation, especially the ovarians, plication of the uterosacral ligaments to relieve congestion in the more deeply situated veins about the uterine artery, and round ligament shortening.

Radium should not be used to check menorrhagia, because there is danger of rupture of the thin-walled tortuous veins; the backache remains unrelieved.

ARNOLD GOLDBERGER

**Erbsloeh, Joachim:** *The Clinical Significance of Skull Fractures of the Newborn*, Arch. f. Gynäk. 165: 73, 1937.

Skull fractures of the newborn can and do result from spontaneous as well as from instrumental deliveries. Such trauma need not be fatal, in fact usually is not. Fatalities and sequelae are usually the results of intracranial hemorrhage and rarely of simple skull fracture. In fact, recovery is complete and uneventful unless there is a resulting hemorrhage somewhere in the central nervous system. Uncomplicated skull fractures are usually symptomless, require no therapy and leave no traces which can be determined roentgenologically. Uncomplicated skull fractures are therefore probably much more common than is generally supposed. The only known complication of simple skull fracture is the "meningocoele spuria traumatica."

RALPH A. REIS.

**Küstner, H.:** *Intracranial Injury of Children During Labor*, Med. Klin. 33: 221, 1937.

Among 7,319 children born in the Leipzig clinic, 453 (6.2 per cent) were born dead or died during the first week. However, of the 5,958 children born spontaneously, only 228 (3.8 per cent) were born dead or died. Of these 228 children, 47 died during labor, were immature or monsters and hence could not have been saved under any conditions. In addition 27 babies died of asphyxia and 14 showed definite cranial trauma. Out of the total of 228 babies, 129 died not during labor but during the first week of life and most of these (76 per cent) perished during the first 2 days. Of these 129 children, however, 104 (80 per cent) were premature. Hence the neonatal death rate of spontaneously born children can be reduced only by preventing premature labor.

The situation is entirely different in the case of operative deliveries. Among the 7,319 children in this series, 1,356 were delivered by operative means and of these, 220 (16.2 per cent) died. Among these 1,356 babies, 1,225 were full term and only 131 were premature. Among the 1,225 full term babies 10.3 per cent were born dead and among the 131 prematures 71.8 per cent died. Some of these children died as the result of illness of the mother.

The author's study leads him to believe that fear of cerebral damage to the newborn during labor is not justified. While it is true that a certain proportion of babies die as a result of such injury, most babies die as the result of other complications which endanger the mother far more. Babies born with cerebral injury should not be treated because while a few recover, most show physical and mental disturbances later in life.

J. P. GREENHILL.

**Brauder, T.:** *Intraeranian Birth Injuries in Breech Deliveries*, Monatschr. f. Geburtsh. u. Gynäk. 105: 205, 1937.

From a study of his own cases and from a review of the literature, Brauder comes to the conclusion that the death rate in breech deliveries is higher in cases where manual aid is used than in cases where the delivery is spontaneous. Likewise the fetal mortality is higher in cases where extraction is resorted to than in cases of manual aid. Autopsies on newborn babies with intracranial hemorrhage show an unusually high incidence of babies born by the breech. The danger in breech deliveries is particularly great in premature babies. Evidences of intracranial hemorrhage are not infrequently observed in babies born breech first and in later life these babies develop epilepsy, spastic paralysis, and imbecility. Among the author's mentally defective twins, the incidence of breech deliveries was very high. One cause for the increased incidence of intracranial bleeding in breech cases is the very rapid delivery of the head through the pelvic canal. The same applies to babies delivered by high forceps and in precipitate labors. Since mental deficiency is so frequent in breech cases and since breech presentations occur in 3 per cent of all labors, prophylactically a breech presentation should often be an indication for cesarean section.

J. P. GREENHILL.

delivery, and 40 per cent after birth, whereas, of the babies weighing more than 2,000 gm., 4 per cent died before labor, 3 per cent died during labor and 10 per cent after birth. Thus of babies weighing less than 2,000 gm., only 31 per cent survived, but of those above 2,000 gm., 83 per cent survived.

J. P. GREENHILL.

**Bruecke, Hans:** The Problem of Injecting Medication Into the Child During Birth, *München. med. Wchnschr.* 83: 2096, 1936.

Bruecke enters into a discussion on the merits and demerits concerning the use of cardiozol during labor for the improvement of fetal cardiac action.

His observations were as follows: Before the use of cardiozol, in 5,864 births, the total of fetal fatalities was 210 (3.60 per cent); after employment of cardiozol, in 9,263 births, the total fatalities were 301 (3.24 per cent). With this difference of only 0.36 per cent, he does not feel that a value of cardiozol has become apparent.

C. E. PROSHEK.

**Cole, W. C. C.:** Obstetrical Influences on the Weight Curve of the Newborn, *Surg. Gynec. Obst.* 68: 179, 1939.

The conception that the "normal" newborn infant may be in a state of mild shock is relatively new. If this proves to be correct, such shock should greatly modify not only our routine care of newborn babies but many obstetric procedures.

A statistical analysis of 996 newborn babies is presented with the view of determining whether obstetric and neonatal procedures influence weight loss in the newborn. It is shown that certain factors tend definitely to increase the loss in weight and that others tend to decrease the loss. It seems conclusive that the weight loss of the newborn is not entirely physiologic. The evidence presented seems to confirm the idea that the "normal" newborn is in a state of mild shock as a result of the trauma of labor. In general, factors which tend to retard or ease the second stage of labor appear to be favorable to the child.

WILLIAM C. HENSKE.

**Clifford, Stewart H., and Irving, Frederick C.:** Analgesia, Anesthesia and the Newborn Infant, *Surg. Gynec. Obst.* 65: 23, 1937.

Opium derivatives administered during labor have been found to exert an unfavorable influence upon the condition of the newborn infant proportional to the amount given and to the time interval between the administration of the drug and the birth of the child. In this group 57 per cent of the infants required some stimulation before they would breathe and cry normally, and 23 per cent were asphyxiated to the point of requiring artificial resuscitation. Successful maternal amnesia was obtained in but 34 per cent of the cases.

The barbiturates have had no harmful effect either upon the life of the fetus or upon the life of the newborn infant. Over 10,000 mothers have received sodium amytal or pentobarbital in the past five years, and during this interval both the stillbirths and the newborn infant death rates have fallen below the level of the preceding five years. Following analgesia through a combination of barbiturate, scopolamine, rectal ether, nitrous oxide-oxygen and small amounts of ether, 37 per cent of the infants required some stimulation before normal respirations were established, while 31 per cent were sufficiently asphyxiated to require artificial resuscitation. Complete amnesia was obtained for 78 per cent of the mothers of this group.

Neither pentobarbital, sodium amytal, scopolamine, rectal ether, nor paraldehyde could be held responsible for the symptoms of asphyxia that were encountered in some of the newborn infants. It is the writers' belief that the untoward effects of analgesia may well be explained by nitrous oxide-oxygen mixtures above the 85:15 level, producing a degree of fetal asphyxia dependent upon the duration of the exposure and the size of the infant.

WILLIAM C. HENSKE.

**Philipps, S.: Hemorrhage and Rupture of the Adrenal in the Newborn Infant, South. M. J. 31: 759, 1938.**

Adrenal hemorrhage in the newborn is a fairly common occurrence, but it is usually discovered only at post-mortem examination. Mention is made of the occurrence of bilateral adrenal hemorrhage in an infant who presented clinical signs suggestive of cerebral hemorrhage which was not verified at necropsy.

The author reports a case of an apparently normal male infant weighing nine pounds at the time of its spontaneous birth. On the fourth day the baby appeared acutely ill. It was lethargic, feverish, had convulsive twitches, and in the right hypochondrium a lemon-sized mass was palpable. In twenty-four hours the hemoglobin fell from 75 per cent to 45 per cent. The child died on the fifth day.

The abdomen was found filled with blood which had infiltrated retroperitoneally, and had forced its way through the diaphragmatic hiatuses into the thoracic cavity. The right adrenal was torn and largely destroyed by hemorrhage into its substance.

The author believes that the salient clinical features in this patient were shock and symptoms of exsanguination. He doubts whether the use of a potent cortical hormone extract in accordance with Goldzieher's hypothesis of acute adrenal insufficiency would have been of value.

ARNOLD GOLDBERGER.

**Fournier, R., and Klein, R.: Twin Pregnancies With Death of One Baby, Bull. Soc. d'obst. et de gynéc. 26: 350, 1937.**

In a series of 20,000 labors the authors found 210 sets of twins. Among the latter, one child was born dead in 13 instances or in 6 per cent of the twins. Among these 13 cases, syphilis was definitely present three times; syphilis was most likely present in six additional cases; one mother had toxemia and in two cases there were numerous infarcts in the placentas. Hence, syphilis caused the death of most of these fetuses.

J. P. GREENHILL.

**Randall, Lawrence M., and Rynearson, Edward H.: Delivery and Care of the New-Born Infant of the Diabetic Mother, J. A. M. A. 107: 919, 1937.**

The mortality among infants born to diabetic mothers has continued high in spite of advanced knowledge in the treatment of diabetes. By subjecting seven successive diabetic mothers to cesarean section between the thirty-third and thirty-seventh weeks of pregnancy, the authors feel they have avoided those dangers which arise during the last few weeks of pregnancy and have saved the mother and child from the risk of a difficult labor. All infants were born alive. The concentration of sugar in the blood of the mother, the infant and the umbilical cord were determined immediately after delivery. Hypoglycemia of the newborn was observed in a few cases and seems to support the view that the child's pancreas continues to overfunction. Whenever twitchings, convulsive movements or cyanosis indicate the development of hypoglycemia, 10 c.c. of a 10 per cent solution of dextrose is given by mouth if possible; otherwise it is administered intramuscularly. The length of the period of danger from hypoglycemia cannot be predicted with accuracy.

GROVER LIESE.

**Whitaker: Anemia and Jaundice in the New-Born, Illinois M. J. 74: 134, 1938.**

The fetus really exists in a state of oxygen want or relative anoxemia. Pure oxygenated blood exists in only one vessel of the fetal circulation, the umbilical vein, coming from the placenta to the fetus. Nature produces an increased amount of red blood cells in response to the relative anoxemia.

It is apparent then that the infant enters this world with a polycythemia, usually showing red cells from 5 to 7 million at birth with correspondingly elevated

Fischer, Eberhard: Later Development of Children Suffering From Birth Trauma Spasms, München. Med. Wehnschr. 85: 1582, 1938.

Follow-up examinations of 18 children afflicted with birth trauma spasms revealed the following results:

Eight children had developed normally, physically and mentally, save for insignificant defects. The family history showed no peculiarities.

Out of five children who died, the cause of death in four cases was a disease of the central nervous system together with spasms which had prevailed ever since birth. It may be assumed, therefore, that the children died as a result of the birth trauma. In the case of one child who died after a vaccination for smallpox it could not be determined whether the previous birth trauma had caused a lowered resistance and thus indirectly had caused death. As to one of these five children, a heredity of the same ailment in the family group could be found and in another case the heredity was questionable.

In the cases of five children with permanent defects, there could be found, besides other disturbances, various degrees of feeble mindedness. The connection of birth trauma and permanent defect was made evident by the continuation of pathologic symptoms. Localized symptoms which permitted of a localization of the brain injury were present in all cases more or less distinctly (Jacksonian epilepsy, speech defects, difficulty of hearing). Thus the brain injury may have caused the permanent defect. Investigations of the family histories have not shown in all cases a heredity for a similar ailment, but a strong predisposition for nervous and mental disturbances could be clearly shown in all cases. Thus it is possible that the pathologic heredity might be the cause of these disturbances. The nervous and mental disturbances of these children could not be attributed to the exogenous factor, the birth trauma, or the endogenous factor, the heredity, alone, as both factors in most cases operate concurrently. How far the factors might influence each other, cannot be determined.

The high number of sick and dead children in comparison to the low number of healthy ones seems to prove that in this investigation one was dealing with severe and definite cases of intracranial hemorrhage so that subsequent disturbances were to be expected in greater numbers.

From the manner of delivery and the clinical symptomatology of the intracranial hemorrhage post partum, no prognosis for the further development could be made.

All the newborns afflicted with intracranial hemorrhage were treated in the same conservative manner, so that the method of treatment could not have caused any difference in the development of the children.

C. E. PROSHEK.

Gordon, G. C.: Persistent Overmoulding of the Skull Bones Causing Fits in an Infant, Brit. M. J. 1: 14, 1938.

The case of an infant having convulsive seizures is reported. One older child was born three and one-half years before and is healthy and normal. This child was born spontaneously after less than one hour of labor. The first convulsions occurred on the fourteenth day. They continued intermittently until the thirty-fifth day. At three months of age, the time when the case was reported, no more fits had occurred. Examination at the time of the first seizure revealed an overlapping of the skull bones at the suture lines and an obliteration of both fontanels. The baby was also blind. Because there was no evidence of paresis, no cutaneous sensory loss, a severe degree of vomiting and a blindness, the author feels that the cause was a generalized increased intracranial pressure from the overmolding of the skull bones rather than from an intracranial hemorrhage. At three months of age, the bones overlapped not any longer, the anterior fontanel was 0.5 inch in diameter, the degree of blindness was decreasing, and the child was apparently recovering.

F. L. ADAIR AND J. A. HAUGEN.

Applications for admission to Group B, Part I, examinations must be on file in the Secretary's office not later than October 4, 1939.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J., on June 7, 8, and 9, 1940, immediately prior to the annual meeting of the American Medical Association to be held in New York City from June 10 to 14 inclusive.

Applications for admission to Group A, Part II examinations must be on file in the Secretary's office not later than March 15, 1940.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Candidates certified by the American Board of Obstetrics and Gynecology by examination, May, 1939, Meeting at St. Louis, Mo.

GEORGE H. AGNEW, Detroit, Mich.

CARMI R. ALDEN, Boston, Mass.

EDWARD ALLEN, Chicago, Ill.

RUSSELL W. ALLES, Detroit, Mich.

A. N. ARNESON, St. Louis, Mo.

FRANZ ARZT, St. Louis, Mo.

EUGENE S. AUER, Denver, Colo.

MAURICE I. BAKUNIN, Bridgeport, Conn.

ARTHUR BAPTISTI, JR., Baltimore, Md.

LESTER E. BAUER, Detroit, Mich.

CLAYTON T. BEECHAM, Philadelphia, Pa.

SOL J. BENENSOHN, Chicago, Ill.

H. ROBERT BERMAN, Newark, N. J.

EDWARD C. BERNELL, Chicago, Ill.

EDWARD M. BLAIR, Vancouver, Canada

OSCAR H. BLOOM, Brooklyn, N. Y.

THOMAS M. BOULWARE, Birmingham, Ala.

WALLACE B. BRADFORD, Charlotte, N. C.

JOHN I. BREWER, Chicago, Ill.

HAROLD M. BRILL, Chicago, Ill.

JAMES M. BROCKMAN, Memphis, Tenn.

RADFORD BROWN, Washington, D. C.

JOHN A. C. BUSBY, Oak Park, Ill.

ARTHUR C. BUTTS, New York, N. Y.

H. E. CANTER, Pittsburgh, Pa.

GLENN A. CARMICHAEL, Butte, Mont.

EAKLE W. CARTWRIGHT, San Diego, Calif.

JOHN CASAGRANDE, Brooklyn, N. Y.

ALBERT E. CATHERWOOD, Detroit, Mich.

N. EDWARD CLAYMAN, Cleveland, Ohio.

HARRY L. CLARK, Brooklyn, N. Y.

GEORGE G. COCHRAN, JR., Brooklyn, N. Y.

R. M. COLLINS, Council Bluffs, Iowa.

HARRISON S. COLLISI, Grand Rapids, Mich.

JAMES R. COSTELLO, Washington, D. C.

DANA W. COX, Columbus, Ohio.

ROLAND S. CRON, Milwaukee, Wis.

JOSEPH G. CROTTY, Cincinnati, Ohio.

WILLIAM J. CUSACK, Washington, D. C.

HAMPTON P. CUSHMAN, Detroit, Mich.

ALBERT B. DAVIS, Camden, N. J.

M. W. DAVIS, St. Louis, Mo.

JOSEPH DEPIETRO, New York, N. Y.

SAMUEL DODEK, Washington, D. C.

EVA F. DODGE, Montgomery, Ala.

WILLIAM A. DWYER, Paterson, N. J.

DOROTHY EDWARDS, Chicago, Ill.

WARD L. EKAS, Rochester, N. Y.

FRANK J. FARA, Cicero, Ill.

GEORGE C. FINOLA, Chicago, Ill.

EDWIN R. FLEMING, Medford, Mass.

PAUL F. FLETCHER, St. Louis, Mo.

CLAIR E. FOLSOME, Ann Arbor, Mich.

OWEN C. FOSTER, Detroit, Mich.

ERNEST W. FRANKLIN, JR., Charlotte,

N. C.

FRANK J. FROSCH, Philadelphia, Pa.

HAROLD A. FURLONG, Pontiac, Mich.

R. A. GANDY, Stamford, Conn.

JOHN Z. GASTON, Houston, Texas.

GEORGE O. GAUEN, St. Louis, Mo.

GEORGE B. GERMAN, Camden, N. J.

O. J. GIBSON, St. Louis, Mo.

JAMES L. GILLARD, Muskegon, Mich.

OSCAR GLASSMAN, New York, N. Y.

ASCHEP H. C. GOLDFINE, Chicago, Ill.

ROBERT H. GOODWIN, New Bedford, Mass.

GRACE V. GORHAM, Norwalk, Conn.

WILLIAM A. GRAHAM, Durham, N. C.

GEORGE B. GRANGER, Rockville Center,

N. Y.

LANAN A. GRAY, Louisville, Ky.

CRAWFORD GRISWOLD, Bridgeport, Conn.

THOMAS W. GRZEBIEN, Providence, R. I.

JOHN D. GUESS, Greenville, S. C.

WESLEY W. HANFORD, St. Louis, Mo.

GEORGE C. HANNA, JR., Philadelphia, Pa.

JAMES F. HANNA, Fargo, N. D.

JOSEPH A. HARDY, JR., St. Louis, Mo.

LEO J. HARTNETT, St. Louis, Mo.

PRESTON HAYNES, Washington, D. C.

CARL HELWIG, Seattle, Wash.

HAROLD HENDERSON, Detroit, Mich.

ERLE HENRIKSEN, Los Angeles, Calif.

CHARLES R. HENRY, Little Rock, Ark.

hemoglobin values. This high count tends to persist during the first week and then slowly falls. There is no need for the increased red cells after birth; they are destroyed and the hemoglobin liberated is broken down into bilirubin, the iron free pigment, and hemosiderin, the iron-containing pigment. The bilirubin value rises, and when it reaches a certain point, visible jaundice results.

Physiologic jaundice, normally in a mild form, appears about the third day or later and tends to clear up in a few days. No bile is noted in the urine. Whenever the clinician has ruled out the ordinary type of physiologic jaundice in the newborn, whatever the cause for the case at hand, the prognosis is serious. Various studies show mortality rates up to 80 per cent. This form may occur sporadically, but is usually familial. It is practically always evident before the third day. The icterus is intense, the infant appears gravely ill, being quite drowsy and usually prostrated. Death may occur quickly. The liver and spleen are enlarged. There is bile in the stools and also in the urine. These cases rarely recover spontaneously. There is usually an associated anemia, the outward signs of which are masked by the intense jaundice, but anemia is not a necessary accompaniment. Extensive hemorrhages may occur from the mucous membranes or into the skin.

Examination of the blood in infants with this type of jaundice is exceedingly important and yields findings almost pathognomonic. The presence of nucleated red blood cells in abnormal numbers is the classical finding. Nucleated red cells should not appear in the peripheral blood of the normal infant after the first week. In these cases, however, one usually finds an increase in immature red cell forms, megaloblasts, erythroblasts, normoblasts and reticulocytes. The characteristic cell is a macrocyte, indicating that the mean diameter of the red cells is increased in icterus gravis. The van den Bergh tests in these cases show a markedly increased indirect reaction, and also a direct immediate reaction, really a biphasic response which implies necrosis of the liver cells.

The pathology noted in cases of icterus gravis consists primarily of a generalized yellowish tint of the various organs and serous surfaces with the essential findings being noted in the liver, spleen, kidneys, and consisting of islands of extramedullary blood formation.

Treatment to date for icterus gravis with or without erythroblastosis consists chiefly in early blood transfusions or the use of maternal serum.

J. P. GREENHILL.

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## Items

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### American Board of Obstetrics and Gynecology

At the recent examinations held by the Board at St. Louis, Missouri, on May 13, 14, 15, and 16, 228 candidates were certified by the Board.

At the annual meeting of the Board, held in St. Louis on May 12, 1939, it was found necessary, on account of increased administration expenses, to increase the application and examination fees. Effective immediately, these are to be as follows: Application fee \$15.00, payable upon submission of application for review by Board. Examination fee \$75.00, payable upon notification to candidate of acceptance of the application and assignment for examination. Neither fee is returnable. This increase does not apply to candidates whose applications were filed prior to May 12, 1939.

The next written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, December 2, 1939, at 2:00 P.M. *The Board wishes to announce that it will hold only one Group B, Part I, examination in this and subsequent years.* Candidates who successfully complete the Part I examinations proceed automatically to the Part II examinations held later in the year.



ABRAHAM B. TAMIS, New York, N. Y.  
 ANN G. TAYLOR, Philadelphia, Pa.  
 RICHARD W. TELINDE, Baltimore, Md.  
 DONALD J. THORP, Seattle, Wash.  
 CHRISTOPHER M. TURMAN, Philadelphia, Pa.  
 MARGARET TYLER, New Haven, Conn.  
 CHARLES B. UPSHAW, Atlanta, Ga.  
 JOHN R. UPTON, San Francisco, Calif.  
 MAGNUS P. URNES, Chicago, Ill.  
 PAUL H. VAN VERST, Oak Park, Ill.  
 JOHN R. VAUGHAN, St. Louis, Mo.  
 EDWARD C. VEPROVSKY, Flushing, N. Y.  
 CLIFFORD V. WARD, Montreal, Canada.  
 WILLIAM W. WALKER, Memphis, Tenn.  
 H. H. WARE, JR., Richmond, Va.

HELMAN C. WASSERMAN, St. Louis, Mo.  
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### Biological Photographic Association

The ninth annual Convention will be held September 14 to 16, 1939, at the Mellon Institute for Industrial Research, Pittsburgh, Pa. The program will be of interest to scientific photographers, scientists who use photography as an aid in their work, teachers in the biologic fields, technical experts and serious amateurs. It will include discussions of motion picture and still photography, photomicrography, color and monochrome films, processing, etc., all in the field of scientific illustrating. Up-to-date equipment will be shown in the technical exhibit; and the Print Salon will display the work of many of the leading biologic photographers here and abroad.

Further information about the Association and the Convention may be obtained by writing the Secretary, University Office, Magee Hospital, Pittsburgh, Pa.

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### American Congress on Obstetrics and Gynecology

Attention is called again to the meeting to be held in Cleveland, Ohio, on September 11 to 15, 1939.

Complete programs for various sections are now available for distribution. Membership subscriptions now total about 1,500, and it is likely that the attendance will reach several thousands. The success of this undertaking seems assured. A feature will be made of the scientific, educational and commercial exhibits.

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puerperal streptococcal infections in the light of the most recent experimental studies on the hemolytic streptococcus. The laboratory techniques discussed in the paper will be given in detail in the appendix.

#### THE CLASSIFICATION OF THE HEMOLYTIC STREPTOCOCCI

Until comparatively recently, the problem of the classification of the streptococci has been a confused one. Much of this confusion arose as a result of the innumerable bases of classification adopted by different observers. One method of differentiation was based on fermentative reactions, another, on the type of disease from which the strains were isolated, another, on the kind of hemolysis produced by different strains and so on. Schottmüller<sup>2</sup> in 1903 first differentiated streptococci on the basis of hemolysis, but it was not until the work of Brown<sup>3</sup> and of Brown and Smith<sup>4</sup> that this system of differentiation was developed in detail. Brown distinguished between strains of streptococci which produced no hemolysis in blood agar plates\* and those which produced either partial or complete hemolysis on the same media. Those strains producing partial hemolysis, such as the pneumococcus and the *Streptococcus viridans*, he designated as alpha, those producing complete hemolysis as beta, and those giving rise to no hemolysis as gamma. The organisms commonly known as hemolytic streptococci all belong in the beta category and in this paper discussion will be limited to this group.

*Dissociation.*—Within the group of beta hemolytic streptococci, the same confusion in classification has prevailed as among the streptococci in general. In the matter of variation or dissociation, for example, very little agreement has been reached until recently. It is not within the scope of this paper to discuss bacterial dissociation but a brief explanation of its significance may be of value to the reader. In 1921, Arkwright<sup>5</sup> studying the colon-typhoid-dysentery group of bacteria found in old cultures two types of colonies. The one he designated "smooth" because of its glossy, shining surface and even edges. The other he termed "rough" because of its dull, uneven surface and irregular edges. It was soon found that smooth strains were more virulent for man and animal than rough strains and that almost all bacteria had the capacity to produce smooth or rough colonies under suitable conditions. Later, a third variant called "mucoid" because of its watery, glistening, mucoid appearance was described. At the present time the three variants, mucoid, smooth, and rough have been described for many bacteria, including the pneumococcus and the streptococcus. The significance of the phenomenon of dissociation for the clinician lies in the fact that there is a definite correlation between variation and virulence. In general, mucoid strains are associated with severe infections in man, smooth strains with milder human infections, while rough strains are rarely if ever responsible for human disease.

In the case of the hemolytic streptococcus Dawson, Hobby and Olmstead<sup>6</sup> have shown that this organism, like the pneumococcus, can exist in three dissociative phases i.e., mucoid, smooth, and rough. In the first phase the colonies are mucoid, the bacteria are encapsulated and the strains producing these forms are usually virulent and possess type-specificity.† In the second phase, the colonies are smooth, the bacteria are not encapsulated, the strains possess little or no virulence, and they may or may not possess type-specificity. In the third phase, the colonies are rough, the bacteria are not encapsulated, the strains are completely avirulent and are lacking in type-specificity.

\*It cannot be emphasized too strongly that the type of hemolysis can be distinguished with certainty only in deep pour plates and in media containing no dextrose since dextrose inhibits hemolysis.

†Depending upon the presence of the "M" substance of Lancefield.

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### THE TREATMENT OF HEMOLYTIC STREPTOCOCCAL INFECTIONS DURING PREGNANCY AND THE PUERPERIUM, WITH SULFANILAMIDE AND IMMUNOTRANSFUSION

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#### INTRODUCTION

THE use of sulfanilamide in the treatment of puerperal infections, especially those caused by the hemolytic streptococcus, is now established on a sound clinical basis. In a series of 106 cases reported by Colebrook and Purdie,<sup>1</sup> the total case fatality rate of sulfanilamide treated cases as compared with the total case fatality rate in puerperal sepsis prior to the use of sulfanilamide has been decreased from an average of 22 to 8 per cent. That this decrease is due to the sulfanilamide and not to a diminution in the virulence of the organism is shown by the fact that the incidence of bacteriemia has remained about the same since the advent of the drug while the fatality rate in treated bacteriemic cases as compared with the fatality rate in untreated bacteriemic cases has been decreased from an average of 71 to 27 per cent.<sup>1</sup> Thus, as a result of this new therapeutic agent puerperal sepsis is no longer the grave obstetric problem it once was. To assume that it is no longer any problem or to rely wholly on sulfanilamide without regard to the bacteriologic aspects of each case would be dangerous because not all strains of hemolytic streptococci are equally susceptible to the action of sulfanilamide. The intelligent management of puerperal infections and the rational use of sulfanilamide in such infections should, therefore, be based to some extent upon a knowledge of the bacteriologic status of the infecting organism and the immunologic status of the patient. The purpose of the present paper is to outline a method of treatment of

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At the present time, owing to the impracticability of producing streptococcal *antibacterial* sera commercially, there is no such serum for clinical use on the market. When specific antibody is needed in the treatment of septic streptococcal infections the only source available is the blood of an immune donor.

*Toxin Production.*—The hemolytic streptococcus elaborates at least 5 filterable exotoxins. These are: (1) hemolysin, (2) leucocidin, (3) erythrogenic toxin, (4) fibrinolysin, and (5) the "spreading factor" of Duran-Reynals.<sup>16</sup> The hemolysin or streptolysin lyses red blood corpuscles *in vitro* and exerts a toxic effect in the animal body. The nature of the leucocidin which is capable of destroying leucocytes *in vitro* is not definitely known. Whether or not it is identical with the streptolysin remains in doubt although the bulk of the evidence would suggest that it is a different substance. Fibrinolysin, as the name implies, possesses the ability to liquify human plasma or fibrin clot. It is elaborated by almost all Group A strains. The filtrates of invasive streptococci contain another toxic substance called the "spreading factor." As yet very little is known about this substance beyond the fact that it increases the permeability of rabbits' skin to suspensions of India ink or to bacterial cells. Menkin,<sup>17</sup> in his studies on inflammatory fixation, has shown that staphylococci tend to be fixed very rapidly in the tissues after subcutaneous injection, whereas streptococci under the same conditions fail to promote the formation of an inflammatory barrier for a much longer period of time. It is highly probable that the spreading factor is involved in this delayed fixation.

The importance of the erythrogenic toxin, which is responsible for the rash in scarlet fever, lies in its ability to produce a potent antitoxin in the animal body. Hooker and Follensby<sup>18</sup> and Hooker<sup>19</sup> have identified two toxins, A and B toxins, in erythrogenic toxin. The A toxin which is identical with the Dick toxin is of greater importance than the B toxin because it is elaborated by almost 90 per cent of the toxin-producing strains. Erythrogenic toxin is neither type-specific nor disease-specific. There is no such thing as scarlatinal erythrogenic toxin as differentiated from the erythrogenic toxin of erysipelas. In the production of commercial streptococcal antitoxin the strain most widely used is Dochez N. Y. 5. Since this strain elaborates both A and B toxins, the antitoxin produced by it will neutralize both toxins. Commercial streptococcal (scarlatinal) antitoxin is, therefore, of value in treating the *toxic* manifestations of any streptococcal infection, regardless of the disease entity.

#### THE MECHANISM OF INFECTION IN HEMOLYTIC STREPTOCOCCAL DISEASES

In the production of disease by any micro-organism two factors are involved, namely, the virulence of the organism and the resistance of the host. The virulence of the hemolytic streptococcus is determined by its ability to invade the host and multiply in the tissues and by its capacity to produce toxins within the body. Invasiveness and toxicity are separate attributes of this organism. Some strains are both highly invasive and toxic but many strains are characterized by a predominance of one or the other. The clinical picture of streptococcal disease varies depending upon which element, the septic (invasive) or the toxic, predominates.

The resistance of the host to invasion by the hemolytic streptococcus depends upon the ability of the host to destroy the organism and to neutralize the toxins produced by it. The destruction of gram-positive cocci is accomplished by the process of phagocytosis and intracellular digestion. In the case of *virulent* streptococci, as Ward and Lyons<sup>14</sup> have shown, phagocytosis by human leucocytes depends upon the sensitizing action of specific antibacterial antibody. The toxic products of the organisms are not influenced by antibacterial antibody and require antitoxin for their neutralization.

*Grouping and Typing.*—With regard to the problem of the serologic grouping and typing of hemolytic streptococci innumerable investigations have been carried out. To Lancefield<sup>7</sup> and to Griffith,<sup>8</sup> however, belong the credit for the most valuable contributions along these lines. Griffith by the technique of slide-agglutination demonstrated that hemolytic streptococci could be differentiated into serologically distinct types. Lancefield using precipitative methods found that these organisms elaborated a type-specific, proteinlike material which she designated the "M" substance, and a group specific antigen, carbohydrate in nature which she named the "C" substance. On the basis of the group antigen, Lancefield found that hemolytic streptococci could be classified into groups according to the source from which they were isolated. All human, pathogenic strains with rare exceptions fell into one group (Group A); strains producing mastitis in cattle into another (Group B); strains from milk and cheese into still other groups, etc. At the present time at least nine\* different groups have been demonstrated by the Lancefield technique. The latest work of Evans and Verder<sup>9</sup> indicates that the Lancefield groups can also be differentiated with a high degree of accuracy by fermentative reactions and sensitivity to bacteriophage B. So far as human pathogenicity goes only Group A strains are of prime importance, although in some instances Group B, C, D, and G have been responsible for human infections. Group D strains have frequently been isolated from the vagina of normal individuals and occasionally have caused mild urinary tract infections.

Both Griffith and Lancefield by the methods already mentioned have subdivided Group A strains into some 25 serologic types. From an immunologic and epidemiologic point of view their work has been extremely valuable but so far has not been of much aid therapeutically because of the practical difficulties inherent in making protective antistreptococcal sera against such a diversity of types. In fact, it has always been extremely difficult to produce even a single type-specific serum with the hemolytic streptococcus. The only vaccines which have been found to stimulate the production of the protective antisera have been those which contained some living organisms. The reason that living organisms are necessary involves a consideration of the antigenic structure of the hemolytic streptococcus in relation to virulence and immunity.

*Virulence and Immunity.*—In 1897, Bordet,<sup>10</sup> studying the hemolytic streptococci, noticed that when guinea pigs were injected intraperitoneally with this organism, most of the cocci were rapidly phagocytosed. The few that remained unengulfed soon developed capsules, continued to resist phagocytosis and ultimately brought about the death of the animal. The development of a capsule appeared to be a mechanism whereby the organism protected itself against phagocytosis and eventual destruction. The work of Todd,<sup>11</sup> Hare,<sup>12</sup> and of Seastone,<sup>13</sup> at a much later date confirmed Bordet's observations. Working independently, each of these investigators correlated resistance to phagocytosis with encapsulation of the organism but pointed out that only in very young cultures or in the animal body were capsules present on the organism. In older cultures (eight to twenty-four hours) the capsules disappeared only to reappear upon transference of some of the culture to fresh medium or injection of some of it into an experimental animal. More light was shed on the mode of destruction of hemolytic streptococci when Ward and Lyons<sup>14</sup> showed that sensitization of virulent streptococci to phagocytosis was brought about by a type-specific antibody or opsonin. This antibody or opsonin against a particular type of organism was found to be present in the blood of certain normal individuals and to a much greater extent in the blood of patients who had recovered from a streptococcal infection caused by the same type. This observation led to the development of a technique for the selection of immune donors for transfusions in streptococcal infections (Lyon<sup>15</sup>). The attempts to produce actively opsonic antisera in rabbits were attended with great difficulty and satisfactory titers were only obtained by repeated injections of living organisms.

\*Sera against Groups A, B, and C have been prepared by Lederle Laboratories, New York, and are now available for diagnostic purposes.

should suddenly regain its virulence. The following case report illustrates some of the above points:

The patient, a 24-year-old, gravida ii, para i, was admitted to the Boston Lying-in Hospital with a diagnosis of incomplete abortion. Three days after admission the patient's temperature rose to 99.6° F. Cervical culture revealed the presence of beta hemolytic streptococci in pure culture. The organism isolated was a Group A strain, but on subculture it was found to be in a nonvirulent phase (S R, i.e., the colonies on Dawson's media were granular and slightly irregular in outline, the cocci were not capsulated, and broth cultures were flocculent). Prontylin was given for two days (80 gr. and 40 gr., respectively) but was discontinued because of a lowering of the red count. Both clinical and serologic evidence indicated that the infecting strain possessed no invasive properties. The patient's temperature never rose above 100° F. and symptoms and physical signs were those of a mild local infection. Serologically, the patient had little or no antibody to her own organism, indicating that the infection was a purely local one with an avirulent organism. One cubic centimeter of her own blood killed only 100 organisms. In spite of continued positive cultures, therefore, a dilatation and curettage was recommended. After a slight postoperative rise the patient's temperature fell to normal, cultures became negative and she progressed rapidly to complete recovery.

In invasive streptococcal infections during pregnancy or the puerperium, highly virulent organisms rapidly invade the tissues and ultimately enter the blood stream unless the infection is controlled before bacteriemia occurs. Recovery in such cases occurs by the process of local fixation plus the development of immune bodies. In untreated cases, if the organism is highly virulent and the patient has no antibodies to that particular strain, invasion of the blood stream takes place very rapidly and death results. If, in untreated cases, the infecting strain is moderately virulent and the patient possesses some antibody to it, local fixation may hold the infection in check until sufficient antibody is developed to prevent bacteriemia or to control it if it occurs.

In the treatment of these infections the chief weapons we possess are sulfanilamide, antibacterial antibody and erythrogenic antitoxin. Although the mode of action of sulfanilamide is still not known, its bacteriostatic effect on the hemolytic streptococcus in vitro and in vivo has been demonstrated by innumerable investigators. Not all strains, however, are equally susceptible to the action of the drug, some are completely resistant (anaerobic strains especially) while others seem to require specific antibacterial antibody in addition to the sulfanilamide for their destruction. The authors, for example, in a recent paper<sup>29</sup> confirmed the observation of Lyons<sup>30</sup> that sulfanilamide and immune serum together had a greater bactericidal effect in vitro on a virulent hemolytic streptococcus than either one alone. The clinical studies of Finland, Brown and Rauh,<sup>31</sup> Keefer,<sup>32</sup> and Lyons<sup>30</sup> on the use of specific antibody with sulfanilamide tend to corroborate these experimental results. The value of the application of experimental observations to clinical problems is illustrated by the following case reports.

Mrs. G. Y., a 24-year-old, para ii, was admitted to the Boston Lying-in Hospital at term with a diagnosis of sinusitis. Three days post partum she developed a septic metritis. Group A, mucoid, virulent hemolytic streptococci were isolated in pure culture from the vagina, nose, and throat. Prontylin therapy was instituted (80 gr. per day). Because the patient's initial response to sulfanilamide was unsatisfactory

The mechanism of infection and recovery in streptococcal disease is determined by the factors mentioned above. In local infections, with organisms of low virulence, for example, recovery takes place through fixation of the infection at the local site without the development of circulating antibodies. In local plus invasive infections with highly virulent organisms (with or without bacteriemia), recovery occurs by local fixation plus the development of immune bodies. The practical application of these general principles to puerperal streptococcal infections will be taken up in a later section.

#### THE ROLE OF HEMOLYTIC STREPTOCOCCI IN PUERPERAL INFECTIONS

Weinstein<sup>20</sup> in investigating the bacterial flora of the vagina of women during normal pregnancy found the incidence of beta hemolytic streptococci to be approximately 4 per cent (17 out of 375 patients). No attempt was made to classify these strains serologically but the fact that none of these patients developed any complications during or following delivery suggests that they were not Group A strains. The earlier studies of Smith,<sup>21</sup> Paine,<sup>22</sup> Colebrook,<sup>23</sup> Hare and Colebrook,<sup>24</sup> Hare,<sup>25</sup> and Lancefield and Hare<sup>26</sup> brought out the fact that *virulent* hemolytic streptococci are rarely present in the vagina of normal parturient women. Lancefield and Hare for example, isolated only 13 strains of beta hemolytic streptococci out of a series of 855 women examined (vaginal culture) before delivery. Of these 13, only 2 strains were Group A strains and only one of the two resulted in puerperal sepsis. Thus the incidence of Group A strains in the human vagina before delivery is only approximately 0.25 per cent. In patients with severe puerperal infections, on the other hand, almost 100 per cent of the strains isolated fall into Group A (44 out of 45 in the series of Lancefield and Hare). All of these studies indicate that in puerperal sepsis infection occurs immediately ante or post partum and as a corollary that such infection is of exogenous and not endogenous origin. That the chief exogenous source is the nasopharynx of contacts was conclusively demonstrated by Colebrook.<sup>27</sup> In an extensive epidemiologic study, she found that approximately 70 per cent of the strains isolated from patients with puerperal sepsis were the same type as the strains isolated from the nasopharynx of attendant contacts or of the patient herself. This work is indirectly confirmed by the fact that Group A hemolytic streptococci, as stated previously are not present normally in the vagina before or after delivery in the absence of a definite infection and that they are not present in the feces of normal pregnant women.<sup>28</sup>

#### METHOD OF TREATMENT OF THE STREPTOCOCCAL INFECTIONS OF PREGNANCY AND THE PUERPERIUM

The normal mechanism of recovery in the streptococcal infections of pregnancy and the puerperium is essentially the same as the mechanism of recovery in streptococcal diseases in general. Local infections with strains of little or no virulence tend to remain confined to the uterus by the process of inflammatory fixation. Organisms of such low invasive power do not produce an antibody response in the body nor is antibody necessary, in general, for recovery from these infections. Treatment of infected abortions caused by noninvasive streptococci should be the treatment of any local infection, i.e., drainage and removal of the focus of infection plus general supportive measures. If the infecting strain in such a case is a Group A organism, sulfanilamide should be given pre-operatively (for dosage, see the following section). This procedure is recommended as a safeguard to the patient in the event that the organism



Three immunotransfusions were given and sulfanilamide was continued. Seventy-two hours after the first immunotransfusion, the patient's temperature reached normal and the infection subsided. The patient was discharged from the hospital twenty-six days post partum.

The chief clinical and bacteriologic findings in this last case are summarized in Table I. Attention is called to the striking response to immunotransfusion, as evidenced by the immediate rise in the phagocytic titer and the killing power of the patient's blood. Another point to be noted is that the content of antibody in the donors' sera, as indicated by their phagocytic titers, was not very great, and yet it was sufficient to produce excellent therapeutic results. This is in line with the experience of Finland and his co-workers,<sup>31</sup> who found that in pneumococcal meningitis small amounts of antibody were highly effective therapeutically when given with large doses of sulfanilamide.

With regard to the use of erythrogonic antitoxin in the treatment of streptococcal infections, the following points are of importance. There is no evidence that antitoxin has any effect on the organism itself and therefore cannot be expected to be of value in the treatment of septic, invasive streptococcal infections. Patients with profound toxemia and an erythematous rash such as in puerperal scarlatina may be relieved of some of the toxic symptoms by erythrogonic antitoxin. Its use, however, should be limited to these cases. In septic and invasive infections, sulfanilamide should be given in large doses.<sup>1, 31, 32</sup> If clinical and serologic evidence indicates that the infecting strain is resistant to sulfanilamide, or if the patient has a positive blood culture and little or no circulating antibody, immunotransfusion is indicated.

Since it has been conclusively demonstrated that the source of infection in puerperal sepsis is exogenous,<sup>27</sup> the necessity for flawless, aseptic technique in the delivery room is further emphasized. If, in spite of such technique, infection occurs, then the evaluation of the patient from a bacteriologic standpoint is prerequisite to rational therapy.

## RECOMMENDATIONS FOR THE TREATMENT OF HEMOLYTIC STREPTOCOCCAL INFECTIONS DURING PREGNANCY AND THE PUERPERIUM

### SUMMARY

- I. Isolation of Organism
  - A. Isolate strain in pure culture (see Appendix I).
  - B. Determine probable virulence (see Appendix I and II).
  - C. Group strain by rapid precipitin method of Brown<sup>33</sup> (see Appendix III).
- II. Management of Patient
  - A. During pregnancy—septic abortion.
    1. If beta hemolytic streptococcus is present in vaginal or cervical culture and patient shows signs and symptoms of a definite infection:
      - (a) Isolate patient
      - (b) Start sulfanilamide. Initial dose should be 0.3 gm. (5 gr.) per 10 pounds body weight. Following initial dose, give 0.6 gm. every 4 hours until a total of 6-8 grams (for an adult of average weight) have been given in the first 24 hours. Thereafter, give a daily maintenance dose of 4 gm. Determine concentration of sulfanilamide in the blood by chemical methods 24 hours after therapy is started. Do daily chemical determinations until level is maintained steadily at 8 to 12 mg. per cent. When level is more or less constant, check blood level every three or four days.

and because her blood contained very little antibody to the infecting strain, immunotransfusion was advised. Four immunotransfusions were given, together with 80 gr. daily doses of prontylin. Five days after the onset of the infection, the temperature reached normal and from then on the patient convalesced rapidly to complete recovery. She was discharged from the hospital nineteen days post partum.

Mrs. M. C., a 37-year-old primipara, was admitted to the Boston Lying-in Hospital at term with a diagnosis of healing pulmonary tuberculosis. Acid-fast infection had been first diagnosed three and one-half years before admission, and sanatorium care had been instituted. Following a thirty-four-hour labor, a midforceps delivery was performed, and because the placenta failed to separate, manual removal was resorted to. Six days post partum, the patient's temperature rose to 104.4° F. Physical examination of the chest suggested renewed activity of the tuberculous process at the right apex. For this reason, uterine and blood cultures were not taken until three days later. Sulfanilamide, in 100 gr. daily doses, was started at this time. On the sixth day after the first elevation of temperature, Group A, virulent hemolytic streptococci were isolated in pure culture from the uterus and the blood stream. Because of the bacteriemia, the antibody content of the patient's blood was determined. It was found that the patient possessed no demonstrable antibody to her own organism. In view of this fact, together with the fact that the patient continued to be severely ill in spite of sulfanilamide therapy, immunotransfusion was advised.

TABLE I

DAY OF DISEASE	CONDITION OF PATIENT	SULFANILAMIDE		IMMUNOTRANSFUSIONS		PHAGOCYTIC TITER OF PATIENT	NUMBER OF BACTERIA KILLED PER C.C. OF PATIENT'S BLOOD
		DOSAGE	BLOOD LEVEL	AMOUNT	PHAGOCYTIC TITER OF DONOR		
1	Onset. Temp. 104.4° F.						
2	Dyspnea, fever, prostration						
3	Condition unchanged						
4	Very septic; blood culture taken	6.6 gm.					
5	No improvement	5.3 gm.					
6	Worse. Oxygen tent. Blood culture reported positive		7.2				
7	Condition unchanged	6.6 gm.					
8	Stuporous. Blood culture taken	6.6 gm.	3.1			0- 0%-25	0
9	Better after transfusion	6.6 gm.	4.4	600 c.c.	44-24%-25*		
10	Improving. Blood culture reported negative	8.0 gm.	5.9	500 c.c.	28-24%-25	61-20%-25	20,000
11	Improving	8.0 gm.	3.9	500 c.c.	35-16%-25		
12	Temp. normal	8.0 gm.	6.4			254-56%-25	300,000
13	Temp. normal; soft diet	8.0 gm.	8.3				
14	Temp. normal; out of oxygen tent	6.6 gm.	4.1				
15	Convalescing rapidly	6.6 gm.					
16	Convalescing rapidly						
17	Convalescing rapidly						

\*The first figure indicates the number of intracellular cocci counted; the second figure, the percentage of cells containing cocci; the third figure, the number of cells counted.

2. Laboratory methods for the rapid isolation and grouping of hemolytic streptococci together with the technique of immunotransfusion are outlined.

The authors wish to express their appreciation to Dr. M. H. Dawson, Dr. Champ Lyons and Dr. J. Howard Brown for permission to reprint the techniques contained in the appendix: to Dr. Rebecca Laneefield and Dr. Dawson for personal advice and assistance; to Dr. Chester Keefer for aiding in the preparation of this manuscript.

#### APPENDIX

##### I. Laboratory Procedure for the Rapid Isolation of Beta Hemolytic Streptococci.—

###### A. Direct isolation

1. Inoculate a tube of blood broth with the swab taken directly from the infected area. (Cervical or intrauterine cultures rather than vaginal ones should *always* be taken whenever possible.) Rub swab over one corner of two blood agar plates and streak for isolated colonies. Incubate one plate aerobically and the other anaerobically.
2. Incubate blood broth three to four hours, then:
  - (a) Plate out a loopful on a blood agar plate, streaking to obtain isolated colonies. Incubate overnight.
  - (b) Dilute serially in sterile broth to 1/100,000, beginning with 0.1 c.c. of undiluted culture. Add 0.1 c.c. of the 1/10,000 and the 1/100,000 dilutions to sterile petri dishes. Then add melted blood agar, mix and cool. Incubate overnight and examine for beta hemolysis.
  - (c) Allow blood broth culture to incubate over night.
3. Examine blood agar streak and deep pour plates for presence of beta hemolytic streptococci.
  - (a) If found in pure culture
    - (1) Note character of growth in broth. In general, mucoid strains grow diffusely in broth, smooth strains diffusely or granularly, and rough strains flocculently.
    - (2) Streak out a loopful of the blood broth culture on a Dawson plate (see Appendix II) and incubate fifteen to eighteen hours. Then examine for type of colony—mucoid, smooth or rough—with a Zeiss colony microscope. Mucoid colonies are large (up to 0.5 cm. in diameter), dome-shaped in contour, regular in outline, and their surface is smooth, glistening and watery in consistency. Smooth colonies are smaller (2 to 3 mm. in diameter), slightly opaque, whitish, fairly regular in outline and their surface is glossy and finely granular. Rough colonies are large (up to 1.0 cm. in diameter), grayish, irregular in outline and their surface is dull, coarse and uneven. Excellent photographs of the various colonial types are reproduced in the paper by Dawson, Hobby and Olmstead.<sup>6</sup>
    - (3) Inoculate 5 c.c. of broth containing 1 per cent dextrose\* with one loopful of the blood broth culture. Incubate eighteen to twenty-four hours and use as the antigen for grouping (see Appendix III).
    - (4) Inoculate a tube of 25 to 50 per cent horse serum neopeptone water with 0.1 c.c. of the blood broth culture. Allow to grow two to two and one-half hours, or until first cloudiness appears, and then do capsule stain as follows. On a clean glass slide mix together one loopful of culture with one loopful of rabbit or human blood, and spread over slide with the edge of

\*Media containing dextrose should never be used in the isolation and identification of hemolytic streptococci except in this instance and in the preparation of the special blood agar plates, as noted below.

- (c) If infecting strain is a Group A, virulent organism and blood culture is positive:
    - (1) Determine antibody content of patient's blood (see Appendix IV and V).
    - (2) If little or no antibody is present in patient's blood, give 300 to 400 c.c. of blood from immune donor (see Appendix IV).
    - (3) Determine antibody content of patient's blood 24 hours after transfusion. If phagocytic index is not significantly increased, repeat immunotransfusion until there is evidence of sufficient antibody response.
  - (d) If infecting strain is a Group A, virulent organism but blood culture is negative, sulfanilamide alone should be effective. If clinical response to sulfanilamide is unsatisfactory after seventy-two hours of treatment, indicating that the strain is resistant to sulfanilamide, give immunotransfusion.
2. If infecting strain is a Group A organism but is *not* virulent according to bacteriological and clinical evidence:
- (a) Isolate patient.
  - (b) Transfuse, if red count is low.
  - (c) Remove focus of infection by doing dilatation and curettage. Probably advisable to give sulfanilamide over a period of twenty-four hours preoperatively. Initial dose of 0.3 gm. (5 gr.) per 10 pounds body weight, followed by 0.6 gm. every four hours until 6 or 8 gm. have been given.
  - (d) Immunotransfusion is not indicated unless bacteriemia develops and antibody titer is low.
3. If infecting strain is a non-Group A organism.
- (a) Isolate patient.
  - (b) If clinical signs and symptoms indicate a definite infection, give sulfanilamide in the above dosages. (There is very little clinical or experimental evidence regarding the susceptibility of non-Group A strains to sulfanilamide. Preliminary results on Groups B, C and G infections in mice seem to warrant further trial in human infections.<sup>1</sup> Infections of the urinary tract with Group D strains are not influenced by the drug.<sup>1</sup>)
  - (c) Nothing is known at present about immunotransfusion in such cases, but theoretically immunotransfusion would be desirable in the presence of bacteriemia with low antibody titer if an immune donor could be found.

#### B. During the puerperium

Follow the plan of treatment exactly as outlined above, with the exception of Section A 2,—i.e., removal of focus of infection. To recapitulate: In puerperal streptococcal infections, give sulfanilamide, give immunotransfusion according to the criteria previously enumerated, and give erythrocytic antitoxin in the presence of marked symptoms of toxemia (cutaneous rash, sustained elevation of temperature, persistently rapid pulse). With regard to immunotransfusion, since *small* amounts of antibody seem to be highly effective in conjunction with large doses of sulfanilamide, much time can be saved by doing the following routinely. Type 10 donors, out of these select the ones having the highest phagocytic indices relative to the patient's phagocytic index, and transfuse as often as necessary with the blood of these donors.

#### SUMMARY

1. A method of treatment of the streptococcal infections of pregnancy and the puerperium based on the most recent experimental observations on the hemolytic streptococcus is presented.

flaming. It may be necessary to centrifuge the serums occasionally to free them from any particles of native precipitate. One should be careful not to form a precipitate by introducing a hot loop into the serum or antigen. Into the lid of the petri dish is placed a disk of moist, but not too wet, white filter paper. With the bottom uppermost, the bottom is placed into the lid of the dish.

*Reading of Results:* The assembled Petri dish is placed bottom up on the stage of a microscope, and the drops are observed through a 16 mm. objective. The optimum illumination for observing particles of precipitate is secured by closing the diaphragm of the condenser until a small (about 2 mm.) spot of light appears on the moist filter paper beneath the drop. With very little experience there need be no question about the interpretation of results. One soon learns to distinguish particles of foreign matter from the specific precipitate. In the serums which I have used, the result is usually apparent within 15 minutes, and in one hour at room temperature, it is fully developed. I have refrigerated the plates over night as a matter of routine, but found no advantage in doing so.

#### IV. Typing and Selection of Immune Donors for Immunotransfusion by the Method of Lyons.<sup>15</sup>—

1. *Determination of Antibacterial Antibody in the Blood of Patients:* About 8 c.c. of blood is withdrawn by aseptic venipuncture and defibrinated by shaking in a flask with glass beads; 0.25 c.c. of blood is measured into a sterile pyrex glass tube 5 cm. long and 9 mm. wide. One drop (about 0.03 c.c.) of a young culture of the streptococcus to be studied is added, the tube sealed in an oxygen flame and rotated for thirty minutes at 16 revolutions per hour at 37° C. The tube is then flamed and broken open, and one drop of the contents smeared as a blood film. This is stained with Wright's stain and examined with the oil immersion lens. A count is made of the number of intracellular streptococci contained in 25 polymorphonuclear leucocytes and the percentage of cells taking part in the phagocytosis is noted. A control slide is usually made from a similar preparation in infant's blood, but this control may be replaced by cultural tests after a little experience.

The bacteria for the phagocytic test are prepared by inoculating one drop of a sixteen-hour broth culture into 4 c.c. of 50 per cent horse serum neopeptone water and incubating until the first clouding occurs, usually from two to four hours.

2. *Selection of Donors for Immunotransfusion:* The blood serum from each of the prospective donors is centrifuged free from cells. To 0.25 c.c. of the patient's blood is added one drop of a given donor's serum. Tubes are so prepared for each prospective donor. The bacteria are added as before, and the test is repeated. The slide showing the greatest amount of phagocytosis indicates the desired donor.

#### V. Method for Determining the Bactericidal Power of Patient's Blood.\*—

Into each of 6 sterile pyrex glass tubes 5 cm. long and 9 mm. wide is measured 0.25 c.c. of whole defibrinated blood from the patient. Care should be taken not to get any blood on the upper part of the tube, as it would be charred when the tube is later sealed. A six- to eighteen-hour 5 per cent horse serum neopeptone culture of the patient's organism is diluted serially in broth from 1/10 through 1/1,000,000. Beginning with the 1/1,000,000 dilution, one drop of each dilution is carefully introduced with the same capillary pipette into each of the pyrex tubes containing the patient's blood. At the time the first drop of the 1/1,000,000 dilution is added to the blood, one drop of the same dilution is introduced into a sterile petri dish from the same capillary pipette. A tube of melted blood agar is added to the petri dish, mixed, cooled and incubated over night. In this way, the number of cocci added to each tube can be estimated. The pyrex tubes are sealed in an oxygen flame, put into a rotating box (for details of this apparatus the reader is referred to Ward's<sup>34</sup> paper) and incubated at 37° C. for twenty-four hours. At the end of this time, the tubes are broken open, the contents mixed well with a capillary pipette, and one drop from each tube is streaked out on a blood agar plate. The plates are incubated over night and the presence or absence of growth is noted on the following day.

\*This technique was originally described by Todd<sup>31</sup> and later was modified by Ward.<sup>34</sup> The method as outlined here is a further modification by the authors.

another slide, as in making a blood smear. Allow to dry and stain with Wright's stain. Encapsulated organisms are best seen along the edges of the smear. Mucoid organisms are encapsulated while smooth and rough are not. This same two-to two-and-one-half-hour culture may be used in the determination of the antibody content of the patient's blood (see Appendix IV).

(b) If not found in pure culture

- (1) Fish beta hemolytic colony from blood agar plate, transfer to 20 per cent horse serum neopeptone water and incubate three to four hours. From then on, proceed as outlined under Section 3a, substituting this culture for the blood broth culture.

B. Indirect isolation (if beta hemolytic streptococcus is picked up on routine vaginal culture).

1. If found in pure culture, proceed as outlined in Section A 3a.
2. If not found in pure culture, proceed as outlined in Section A 3b.

## II. Preparation of Blood Agar Plates by the Method of Dawson, Hobby and Olmstead.\*—

To 3 pounds chopped beef, add 3 liters water. Extract in ice box over night. In the morning, boil for fifteen minutes. Then filter through cloth or cotton towel. Add 12 gm. of sodium phosphate ( $\text{Na}_2\text{H PO}_4$ ). Heat to boiling. Add 2 N NaOH to pH 8.0 (55 c.c.). Boil thirty minutes. Add sufficient water to 3 liters. Readjust to pH 8.0. Boil fifteen minutes. Add 45 gm. of agar, and dissolve. Add 30 gm. of neopeptone (Difco). Readjust to pH 7.8. Flask in 170 c.c. amounts (250 c.c. flasks). Autoclave at 15 pounds for twenty minutes. To each 170 c.c. of agar, add 1.7 c.c. of 20 per cent solution of sterile dextrose and 4.25 c.c. of rabbit (or horse) blood. Pour about 35 c.c. of mixture over a layer of cold infusion agar in a petri dish. This will give 5 plates for each flask. Use fresh, moist plates (not later than two or three hours after pouring).

## III. Grouping of Hemolytic Streptococci by the Method of Brown.<sup>33</sup>—

*Preparation of the Antigen:* The culture is grown in 5 c.c. of infusion broth containing 1 per cent of dextrose for from eighteen to twenty-four hours at 37° C. Many strains grow in the form of a sediment at the bottom of the test tube; others need to be centrifuged. All but about 1 c.c. of the supernatant broth is pipetted off and discarded. Two drops of metacresol purple indicator (0.04 gm. dissolved in 60 c.c. of 95 per cent alcohol and then diluted to 100 c.c. with distilled water) are added to the remaining sediment suspension. From a drop bottle, 2 per cent hydrochloric acid (about 6 per cent concentrated hydrochloric acid) is added, until the indicator turns slightly pink (about pH 3.0). The tube of sediment is heated in a boiling water-bath with occasional shaking for fifteen minutes and then cooled in running cold tap water for ten minutes. From a drop bottle, 2 per cent sodium hydroxide is added until the color of the indicator passes through yellow and just begins to darken (about pH 7.5), but should not be noticeably purple. The tube is then centrifuged for about fifteen minutes and the clear supernatant used for the precipitin test. I have not found it necessary to dilute the antigen.

*Technique of the Test:* On the bottom surface of a nearly optically perfect petri dish (a satisfactory brand of such dishes is known as "Plano") rule 12 mm. squares by means of a wax or diamond pencil. On the abscissa indicate the serums to be used; e.g., A, B, and C. On the ordinate indicate the antigens. Both inside and outside surfaces of the bottom of the petri dish must be very clean and free from lint, dust and finger prints, but need not be sterile. Within the appropriate squares and on the inside surface of the bottom of the dish, place one small (2 mm.) platinum loop of antigen and one loop of serum, mixing the serum with the antigen as added, so as to make rather flat hanging drops when the dish is inverted. A platinum loop is specified because some of the cheaper substitutes give off alkali. To avoid carbon particles in the drops, it is essential to burn off the loop thoroughly, preferably after dipping it into water to remove most of the serum each time before

\*Personal communication.

is by studying the state of affairs antecedent and subsequent to the "toxemia." Such study reveals the fact that about 80 per cent of the women designated as having "toxemia" actually have chronic vascular or renal disease before and after the gravid state, and an additional 5 per cent have such disease in acute form (Table I). However, the remaining

TABLE I. APPROXIMATE INCIDENCE OF VARIOUS DISORDERS IN WOMEN ADMITTED AS "TOXEMIA" OF PREGNANCY

	PER CENT
"Essential hypertension"	60
Chronic nephritis (including glomerulonephritis, pyelonephritis, and polycystic kidneys)	20
Acute nephritis (usually pyelonephritis)	5
Water-retention toxemia	15

15 per cent of such women have had no demonstrable abnormality before pregnancy nor after the pregnancy in which abnormalities called "toxemia" occurred. Further, these women under proper management will have subsequent uneventful pregnancies. It is this group for which the designation "water-retention toxemia" seems appropriate.

#### CLINICAL ASPECTS

The clinical picture manifested by these women is characterized, first, by the absence of apparent abnormalities before gestation and after the puerperium and, second, by a fairly typical course. In the last trimester of pregnancy a rapid gain in weight, generally but not always manifest as edema, is followed by a rising blood pressure, albuminuria, and later symptoms such as headache, visual disturbances, vertigo, epigastric pain, convulsions, and coma. The urine is generally of high specific gravity and does not contain red blood cells or white blood cells until the disorder has existed for some days at least. The nonprotein nitrogen and the ieteric index are always normal or lower than normal until the condition is far advanced. The retinal arteries *never* show the changes that are observed so commonly in women with chronic vascular or renal disease. It is to be emphasized that these cases comprise only one-sixth of the total so-called "toxemias," and that the typical clinical course is not necessarily diagnostic. Other conditions may simulate it closely.

#### WATER METABOLISM

Formerly water retention in pregnancy was considered of "toxic" origin; later the pituitary antidiuretic hormone became the culprit. Now the fashion is to incriminate other, newer hormones. Evidence for these indietments, or for changes in the upper or lower urinary tract being primarily responsible, is lacking.

Almost half a century has elapsed since Starling<sup>3</sup> first postulated the mechanism of water exchange between the blood plasma and the tissue spaces. He indicated that the colloid osmotic pressure exerted by the plasma proteins was the force which prevented the intracapillary hydrostatic pressure from filtering water out of the blood. If one could per-

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## TOXEMIA OF PREGNANCY\*

## TYPES, ETIOLOGY, AND TREATMENT

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THE term "toxemia of pregnancy" has served for generations and still serves as a diagnostic wastebasket to cloak ignorance. Medical prepossession with mysterious and unidentified "toxins" has prevented intelligent study of the various disorders combined under this misnomer. However, writers have wisely refrained from defining what toxemia is. To each the word carries certain connotations; rarely does it mean quite the same thing to any two. The late John Whitridge Williams<sup>1</sup> years ago pointed out that totally different pathologic conditions may be accompanied by identical clinical manifestations and, further, that classification could not be based upon the occurrence of urinary abnormalities, hypertension, coma, or convulsions. Zimmerman and Peters<sup>2</sup> and others more recently have shown that at necropsy patients with identical clinical syndromes may show widely varying or no significant pathologic lesions. There remains, however, one simple method of dividing this heterogeneous group of "toxic" women into at least two main classes, and that

\*Read at a meeting of the New York Obstetrical Society, January 10, 1939.



## WATER METABOLISM IN THE LAST TRIMESTER OF PREGNANCY

The following observations were all made in the last trimester of gestation upon women who were in the hospital but not confined to bed. They comprised both normal pregnant women and those with various types of "toxemia." None had acute glomerulonephritis, congestive heart failure, or anemia. No observations were begun until after the women had stabilized their water balances over a period of at least three days on the ward during which time salt and water were allowed freely but no saline cathartics or bicarbonate of soda were given. Twenty of the women were then given 6.3 gm. of sodium daily, either as 16 gm. of sodium chloride or 23 gm. of sodium bicarbonate in addition to the salt in or on their food. Water was allowed freely. Each of these women

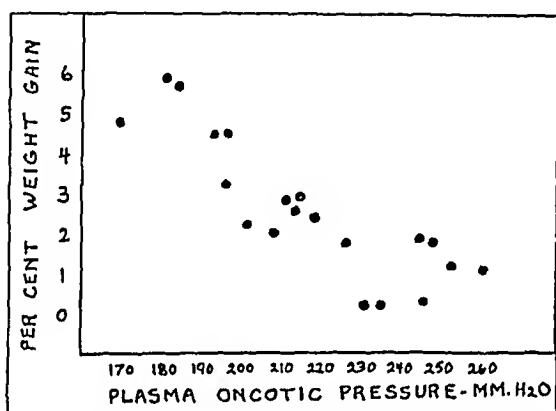


Chart 1.—The percentage body weight gain in three days plotted against the osmotic pressure of the plasma proteins in 20 women in the last trimester of pregnancy who received 6.3 gm. of sodium daily in addition to that taken in or on their food.

retained water as illustrated by their weight changes which are plotted (Chart 1) against their respective plasma protein osmotic pressures. The excellent linear correlation excludes the necessity of involving hormones, hydronephroses, or toxins to explain why some women gained 10 or more pounds and others but one or two. The limiting factor clearly appears to be the plasma protein osmotic pressure.

The converse of these observations was then carried out. Thirty women were deprived of sodium. This was most simply accomplished by arranging that their food consisted each day of only 1,500 c.c. of skimmed milk. Water was allowed freely. Fifteen hundred cubic centimeters of skimmed milk contains but 0.5 gm. of sodium and 2.0 gm. each of potassium and calcium. Each of these women lost weight as a result of moderate to extreme water diuresis. At most, 1 to 2 per cent of the weight loss can be accounted for by an insufficient calorie intake. The amount lost in five days, plotted again as the percentage of original body weight, varied in linear correlation inversely with the plasma protein osmotic pressure (Chart 2). Those women who had visible edema (about half of the group) lost all trace of this. Again there is no need of

fuse an intact human being with a protein free plasma at normal intracapillary pressure it would require approximately ten seconds to filter out the entire water content of the plasma through the 6,300 square meters of surface presented by the capillaries of an average size man. However, the problems of water metabolism involve many other factors. At any level of plasma proteins, the administration of a few grams or more of sodium will cause water retention, and the withdrawal of sodium from the diet will cause water to be lost. This is true both for man and laboratory animals. It is only the magnitude of the change which varies inversely with the level of the plasma protein osmotic pressure. Furthermore sodium, although the most important substance, is but one of the electrolytes involved in water exchange. An increased potassium intake favors sodium and water excretion, and a low potassium intake probably favors water and sodium retention. The administration of any of the salts which result in an excess of negative ions in the body, such as ammonium chloride and nitrate, calcium chloride, or magnesium sulphate, causes sodium and water to be excreted.

The oral administration in large quantity of a freely diffusible organic solute such as urea, other factors being kept constant, will result in a loss of water and salt, as will the intravenous administration of hypertonic glucose or a nonmetabolizable sugar such as sucrose.

A restricted intake of water tends to cause a loss of body sodium and other salts in order to prevent concentration of the electrolytes in the body fluids. A great increase in water ingestion without an increase in electrolyte intake may actually flush out sufficient salts in the urine to result in subsequent depletion of the body fluids and later dehydration.

Other factors being kept constant, the loss of salt and water in increased sweating or diarrhea may result in dehydration.

Anemia, for some unknown reason, is conducive to water retention, as is also increased capillary permeability, such as is encountered in acute glomerular nephritis. Any process which raises the intracapillary pressure, such as congestive heart failure or venous obstruction, favors water retention. Changes in the dietary constituents, as for example the amount of carbohydrate ingested, may influence water exchange. Primary renal failure is but rarely involved in the causation of edema, which most generally depends on "pre-renal deviation." It is thus apparent that water exchange is a complex phenomenon dependent on many factors, any one of which can be studied, provided the remainder are kept constant.

In the nonpregnant subject or animal, as noted above, the magnitude of the water gain or loss following an alteration in electrolyte intake, varies inversely with the level of the osmotic pressure exerted by the plasma proteins, the albumin fraction being four times as osmotically active as the globulin fraction. The determination of the total plasma protein is therefore of no value unless the separate fractions are measured. Nor are these determinations of value unless done by an accurate method by an experienced and competent individual. Refractometric and specific gravity determinations are nearly useless as a means of estimating the colloid osmotic pressure of the plasma proteins.

## THE EFFECT OF CHANGES IN WATER BALANCE ON BLOOD PRESSURE

What is the effect of changes in water balance on arterial hypertension, albuminuria, and pre-eclamptic symptoms? First were studied 10 women in the last trimester of gestation who had normal plasma proteins and either normal blood pressures or known pre-existing "essential hypertension." Chart 3 is characteristic of this group. The administration of the stated amount of sodium resulted in small increments of water retention but was without effect on the arterial blood pressure, urine, or symptoms if any existed.

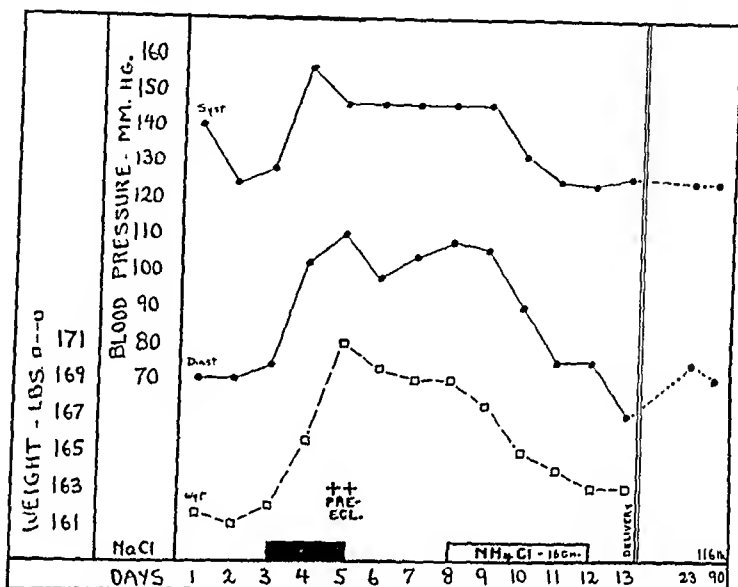


Chart 4.—The effect of sodium administration in a pregnant woman with a plasma protein osmotic pressure of 193 mm.  $H_2O$ . Note the development of acute arterial hypertension and pre-eclamptic symptoms. Generalized edema appeared. No remission occurred during 3 days after sodium was stopped. The administration of 16 gm. of ammonium chloride daily resulted in prompt diuresis and the return of the arterial blood pressure to normal. Symptoms and edema disappeared. Note normal blood pressure after the puerperium.

In contrast to these observations those made on 10 patients with low plasma proteins are illustrated by a characteristic ease in Chart 4. In these patients, the administration of sodium resulted in significant gains in weight, the occurrence of obvious edema, hypertension, increasing albuminuria, and in three instances such pre-eclamptic symptoms as headache, visual disturbance, vertigo, and epigastric pain. Further, when retained water could be eliminated as shown in the chart all these manifestations subsided.

This set of observations represents as far as I am aware the first successful attempt to produce "toxemia" of pregnancy. However, I am sure that many obstetricians can recall patients whose acutely developing "toxemia" followed on a period of heartburn, self-treated with baking soda, or after a fine shore dinner rich in sodium chloride. I have personally observed 11 patients who self-treated their heartburn with bicarbonate of soda, citrocarbonate, or with a patent medicine rich in alkaline salts, only to develop edema, hypertension, albuminuria,

invoking toxins, hormones, or renal disturbances to explain these changes in water metabolism.

It is thus apparent that in these cases of both normal and "toxemic" pregnancy, in the absence of severe anemia, congestive heart failure, and acute glomerulonephritis, water retention, depend essentially on the level of the plasma protein osmotic pressure and the electrolyte intake. These observations must not be construed as meaning that every instance of water retention in pregnancy is due to alterations in these two factors, nor must one factor be considered of greater importance than the other. However, it may be stated that water retention in pregnancy does not differ from water retention in the nonpregnant.

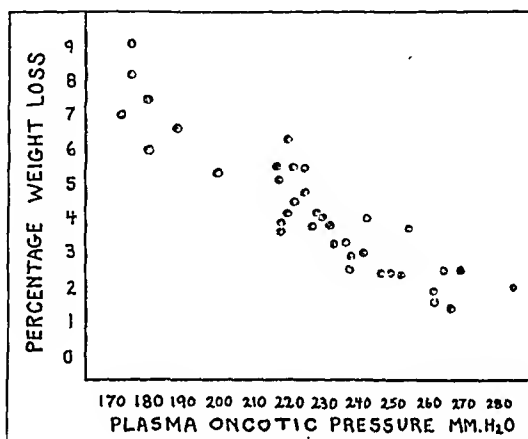


Chart 2.—The percentage body weight loss in five days, plotted as in Chart 1, in 37 women in the last trimester of pregnancy who received 1500 c.c. of skimmed milk daily but no other food. Water was allowed freely.

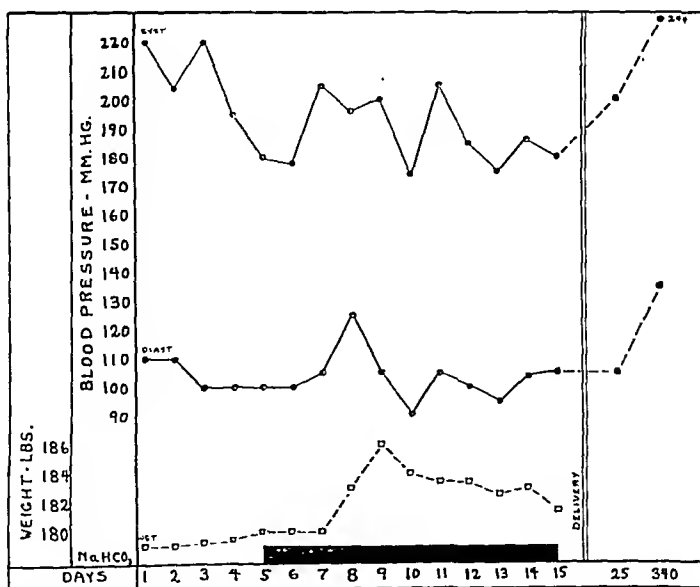


Chart 3.—The lack of effect of sodium administration in a pregnant woman with essential hypertension and a plasma protein osmotic pressure of 230 mm. H<sub>2</sub>O. Note the continued hypertension after parturition.

In contrast to such data are the results obtained in a similar-sized group of women with acute "toxemia" conforming to the clinical and laboratory picture noted earlier under the heading, "Clinical Aspects." These women all had lower plasma proteins than normal but did not have extremely low levels. The data for one case are given in Chart 6 and are characteristic for this group. Diuresis was accompanied by the disappearance of edema and pre-eclamptic symptoms, and the return of the blood pressure to the normal range. All these women had normal blood pressures and negative urinalyses when rechecked several months after delivery.

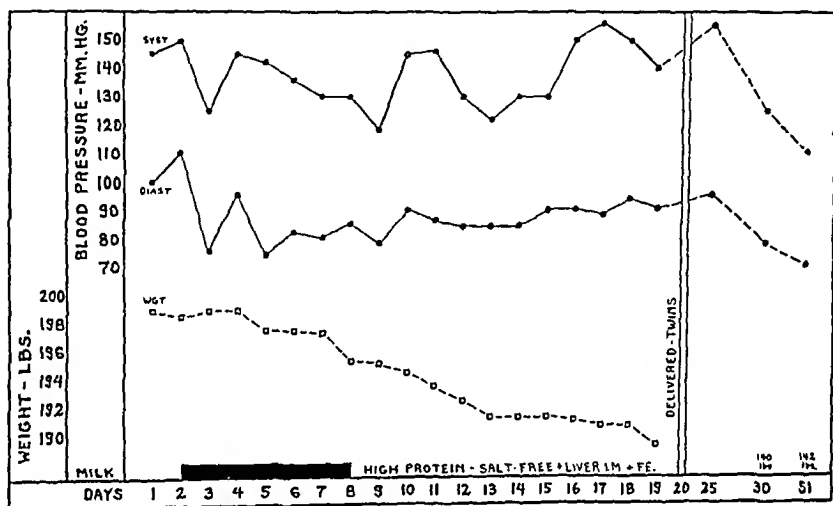


Chart 7.—The lack of effect of a low sodium regime (milk diet) in a patient with a very low plasma protein osmotic pressure (158 mm.  $H_2O$ ) and severe anemia ( $Hg \approx 45$  per cent). Although this patient lost 9 pounds in seventeen days she continued to have massive edema and hypertension. Following delivery the total weight lost in ten days was 50 pounds. Coincidental with this the blood pressure fell to normal.

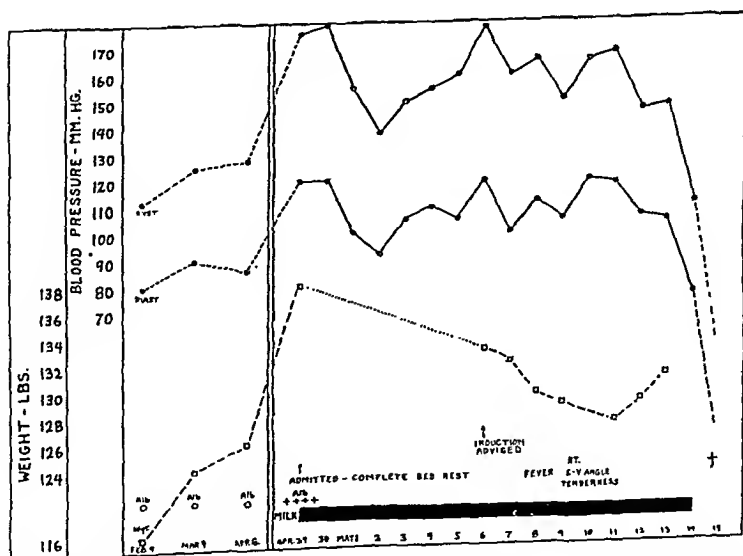


Chart 8.—The lack of effect of a low sodium regime in a patient with acute pyelonephritis. See text.

and, in a few instances, convulsions. In one patient no other treatment than the omission of the self-administered soda resulted in complete remission of all signs and symptoms.

The converse of these observations has also been carried out. Twenty-five women in the last trimester of pregnancy suffering from essential hypertension or chronic nephritis (including one case of congenital polycystic kidneys) have been deprived of sodium by means of the skimmed milk regime noted above. No beneficial results were observed. Chart 5 is characteristic.

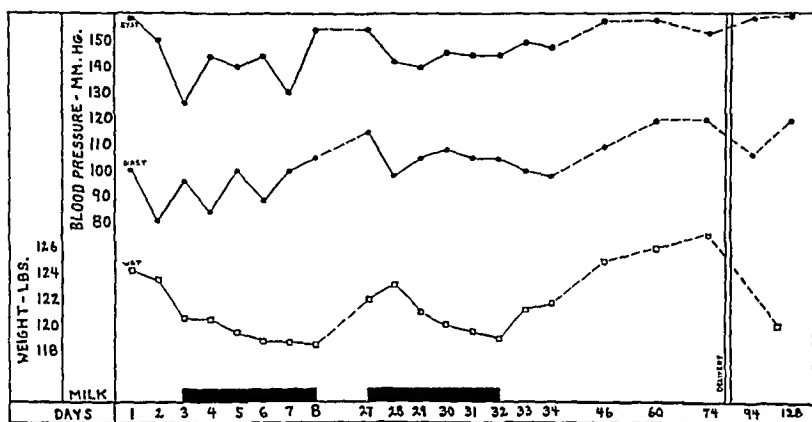


Chart 5.—The lack of effect on blood pressure of a low sodium regime (1,500 c.c. of skimmed milk daily) on two occasions in a pregnant woman with congenital polycystic kidneys. Note continued hypertension months after delivery. Plasma protein osmotic pressure 247 mm.  $H_2O$ .

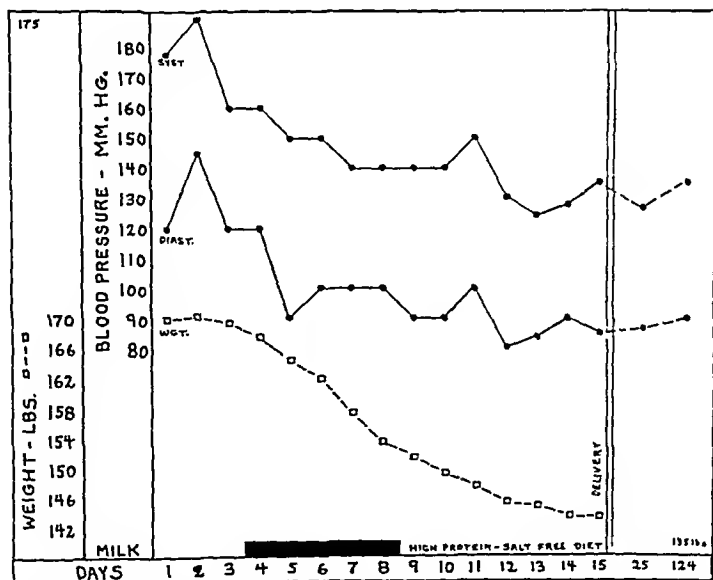


Chart 6.—Marked fall in blood pressure during low sodium regime in moderately severe case of water retention "toxemia" of pregnancy. Note the stationary weight and blood pressure during the control period before the milk regime was commenced, and that the weight remained down and the blood pressure normal while the patient received a diet containing 150 gm. protein and essentially no salt; postpartum the blood pressure remained normal. The plasma protein osmotic pressure was 175 mm.  $H_2O$ .

next pregnancy. Patients with water-retention "toxemia" are prone to have recurrence unless special attention is paid to their protein and electrolyte intake in the next pregnancy. Ten such women have been followed through two pregnancies. They all had hypertension in the pregnancy for which they first were under observation. Four fetal deaths occurred. In the next pregnancy a high protein intake was commenced early. In spite of this an abnormal lowering of the plasma proteins occurred in three. These women were then maintained on a salt-free regime. None of the 10 developed any manifestations of toxemia. Ten healthy babies were delivered. The maximum blood pressures in the two pregnancies are shown in Table II.

It thus appears that water-retention toxemia need not recur in subsequent pregnancies if adequate attention is paid to diet and electrolyte intake.

#### DISCUSSION

Sixty-five years ago Rosenstein stated his belief that eclampsia resulted from the effusion of serum out of a "too-watery" blood. Many methods of treatment of "toxemia" which have met with more or less success, have knowingly or unknowingly been measures to eliminate water retention. The use of purgation with magnesium sulphate to rid the body of "toxins" is a double means of ridding the body of water, first by direct loss from the bowel, second by the acidifying diuretic action of the absorbed sulphate ion. The adherents of the belief that "toxemia" arose from hypocalcemia have administered calcium chloride, an excellent acidifying diuretic. Fluid restriction popularized by Arnold and Fay<sup>4</sup> is obviously aimed at the loss of water. An exceedingly large intake of water, as noted above, may lead to actual diuresis above the amount ingested. Hypertonic glucose solutions given intravenously are dehydrating. Starvation results in a loss of salt and water. A high protein intake may be diuretic because of the increased urea excretion. If the high protein intake is achieved by a large ingestion of meat there will be a relatively high potassium and low sodium intake. A milk regime achieves similar ends.

Why, then, have these methods failed to meet with universal success in the treatment of "toxemia"? First and foremost is the fact that 85 per cent of the cases of so-called toxemia are unrelated to water retention. This fact cannot be stressed too strongly. Second, many cases of water-retention toxemia have plasma-protein levels so low that no method will achieve significant water loss. Third, cases of water-retention toxemia may be complicated by other factors as noted above. Fourth, all methods of ridding the body of excess water are not equally successful and may have harmful side effects. Last, since the aim of the obstetrician has not been clear, he not infrequently has employed measures which counteract each other. The commonest of these is the employment of a salt-free diet, while saline solutions are being given under the skin or intravenously, or bicarbonate of soda by mouth.

Although the most satisfactory clinical measure of water balance is the weight curve, it is to be remembered that all undue gains in weight

It thus appears that one may not only produce this type of "toxemia" by administering sodium but one may relieve it by eliminating sodium, if this results in a loss of retained water. However, if the plasma protein level is extremely low, significant diuresis cannot be produced in non-pregnant subjects by such a procedure. This is likewise true in pregnancy. Chart 7 illustrates the course of events in a woman who continued to have massive edema in spite of sodium restriction, and who showed no beneficial effects from the regime.

Furthermore one may have additional complications as shown in Chart 8.

This patient, a primipara, appeared normal on her first three visits to the prenatal clinic. Three weeks after the last visit she was admitted with edema, hypertension, and albuminuria, having gained 12 pounds in three weeks. It is of interest, however, that the urinary sediment showed many white blood cells and a few red blood cells. The milk regime and complete bed rest did not benefit her. Induction of labor was advised but refused. Following this she developed fever and later slight costo-vertebral angle tenderness. Pyelograms were made (by Dr. Benedict F. Boland) which showed marked dilatation of the right ureter and renal pelvis. Death occurred as a result of aspiration of stomach contents under anesthesia at parturition. The necropsy revealed an extensive acute right pyelonephritis with multiple cortical abscesses, and a normal left kidney. Whether this case represents: (1) water-retention toxemia complicated by acute pyelonephritis, (2) acute pyelonephritis complicated by water-retention toxemia, or (3) acute pyelonephritis alone, cannot be stated definitely. It does, however, illustrate the extreme difficulty of differential diagnosis which may occur.

#### THE EFFECT OF WATER-RETENTION "TOXEMIA" ON SUBSEQUENT PREGNANCY

Patients with chronic vascular or renal disease during one pregnancy will manifest these disorders not only after parturition but also in the

TABLE II. THE EFFECT OF PROTEIN AND SODIUM CONTROL ON THE SUCCEEDING PREGNANCY IN 10 WOMEN WITH WATER-RETENTION TOXEMIA

NUMBER	PREGNANCY WITH TOXEMIA			SUCCEEDING PREGNANCY*		
	MAXIMUM BLOOD PRESSURE MM. HG		PLASMA PROTEIN OSMOTIC PRESSURE MM. H <sub>2</sub> O	NO TOXEMIA		PLASMA PROTEIN OSMOTIC PRESSURE MM. H <sub>2</sub> O
	SYST.	DIAST.		SYST.	DIAST.	
1	146	110	182	120	80	248
2	172	116	180	116	84	252
3	170	110	218	130	80	235
4†	190	145	175	130	90	241
5†	172	112	192	124	82	242
6	170	120	-	130	85	242
7	206	120	-	126	80	219
8†	170	100	-	104	60	-
9†	170	115	183	130	90	215
10	162	120	120	110	70	204

\*Patients 1 to 6 were given an adequate protein intake without salt restriction; Patients 7 to 10 also were maintained on low salt diets.

†Fetal death occurred in Cases 4, 5, 8, and 9 in the "toxic" pregnancy. There was no fetal mortality in the succeeding pregnancy.

In the "toxic" pregnancy each of the 10 women had albuminuria and pre-eclampsic symptoms. In the next pregnancy the patients were asymptomatic and did not have albuminuria.



increase in blood volume, a 50 per cent increase in cardiac output, a moderate elevation of venous pressure, and probably moderate mechanical pressure by the enlarged uterus on the ureters and on the renal veins. Although various tests fail to reveal any consistent changes in renal function in "toxemia" of pregnancy, the fact that albuminuria is generally present in itself indicates that there is a disturbance of the kidney even though histologic examination fails to reveal anything more than cloudy swelling. The real nature of this disturbance and its possible relationship to the occurrence of hypertension as a result of water retention are unknown. The role of hormonal changes in pregnancy is so little understood that discussion is hardly warranted. It is possible that hormonal changes make the pregnant woman unusually susceptible to changes in water balance. However, no one has yet produced toxemic manifestations by administering hormones, and a recent investigation<sup>6</sup> indicated that restoration of hormone values to normal failed to influence toxemic manifestations.

Since hypoproteinemia is one of the more important factors which permits the development of water retention, adequate prenatal care must include attention to the prevention of this condition. Although disturbances of absorption, assimilation, manufacture and urinary loss of protein may be involved, it appears that the chief cause of hypoproteinemia in pregnancy lies in inadequate dietary intake of protein of good biologic value, especially in view of the increased demands for protein for the developing fetus and also for the maternal organism. It is, therefore, of paramount importance that the diet in pregnancy contain more, not less, protein than an adequate diet for nonpregnant subjects. It is likewise important that the pregnant woman avoid an excessive intake of sodium salts under any conditions, and if she has low plasma proteins actual sodium restriction must be employed. Anemia, which is conducive to water retention, is to be avoided by proper prophylactic measures.<sup>6</sup>

#### CONCLUSIONS

1. The term "toxemia of pregnancy" is a misnomer. Approximately 85 per cent of patients so classified actually have primary vascular or renal disease. In such patients changes in water balance do not affect signs or symptoms.

2. A large proportion of the remaining 15 per cent are suffering from water retention. This may be due primarily to low plasma proteins or to excessive sodium intake or, in many instances, to both factors. Measures which lead to further water retention increase the severity of the "toxemic" manifestations, whereas measures which result in the loss of excessive retained water result in an amelioration of these manifestations.

3. A low sodium intake is one means of eliminating undue water retention.

4. The development of water-retention toxemia may be prevented by maintaining the pregnant woman's plasma proteins at a normal level by an adequate diet and avoiding excessive sodium ingestion.

(Detailed descriptions of the observations noted in this paper and a more complete bibliography will be found in references.<sup>7b, d, e, g, h</sup>)

are not dependent upon water. I have seen two patients during pregnancy gain 50 and 72 pounds, respectively, not because of water retention but from true fat accumulation. A low sodium regime was obviously ineffective in ridding the body of excess of fat.

The doctrine that there is a critical level of the plasma proteins below which edema occurs was a necessary stage in the development of our knowledge. However, we have seen patients with plasma proteins far below this level who had no edema because they did not ingest the necessary salt and water to allow the formation of edema. On the contrary, other patients, because of a very large intake of salt and water, have developed generalized edema with plasma proteins well above the so-called critical level.

Why some patients may have rather marked water retention without arterial hypertension is unknown. In a number of instances marked water retention has been observed for a period of several weeks before arterial hypertension developed, and in others parturition has supervened without hypertension ever appearing. Whether these women would have eventually developed hypertension had pregnancy continued longer cannot be said. Although there is no evidence for such a belief, it is possible that some individual or constitutional susceptibility to hypertension is necessary in order that water retention may produce hypertension during pregnancy.

It is to be remembered that although a low sodium regime may free the patient of retained water, result in a fall of arterial blood pressure to normal, and cause headache, drowsiness, vertigo, and visual disturbances to disappear, such a regime does not alter the fundamental disturbance: hypoproteinemia. These patients remain in unstable equilibrium as long as the plasma colloid osmotic pressure remains at a level at which it is constantly in danger of being overbalanced by the intracapillary hydrostatic pressure. "Cure" is not effected until the plasma proteins have returned to normal. Since "toxemia" occurs late in pregnancy, when fetal demands for protein are large, and since hypoproteinemia probably signifies not only a low plasma protein level but also a depletion of the organism's reserve stores of protein, one must not expect a rapid increase in plasma protein values during the remainder of gestation even with intensive protein feeding. It is possible that the intravenous infusion of concentrated plasma protein ("lyophile" serum) may be of value. However, any procedure which alters the blood volume of such patients may upset their unstable equilibrium and precipitate serious results.

A question which inevitably must arise is whether nonpregnant individuals with similar hypoproteinemic edema show the same phenomena regarding blood pressure as do these women. It is true, of course, that the usual type of nonpregnant patient with hypoproteinemia seen in American hospitals suffers from cirrhosis, nephrosis, anemia, tuberculosis, colitis, or other debilitating disease which may alter the reactivity of his vascular system. However, it appears probable that certain peculiarities of the pregnant state itself may be responsible for this unusual behavior of the vascular system to water retention. Some of the known physiologic alterations which are present in pregnancy are a 40 per cent

and today it is accepted that normal pregnancy is associated with a decrease of total serum proteins of from 5 to 7 per cent.

We have done a certain number of total serum protein determinations on pre-eclamptic and eclamptic patients. Although I appreciate fully the importance of the rôle that serum proteins may play in the conduct of water balance, so far I have been unable to convince myself that a reduction in the total serum proteins is responsible for the marked increase in body weight due to water retention that we see in many cases of pre-eclampsia. You are all familiar with many cases like the one Dr. Strauss showed here where the patient's weight is normal during three or four visits to the antenatal clinic and then suddenly there is a marked increase in body weight. There seems to be some factor, of which we are still ignorant, responsible for this sudden water retention.

There is great confusion in regard to toxemias of pregnancy, although this appears to me to be unnecessary. There are two entities that must not be confused with the toxemias of pregnancy; one of them is essential hypertension, and the other, renal disease. First, essential hypertension, whether on a familial, hormonal, nervous or any other basis is a wholly different entity from what we call "toxemia of pregnancy." Second, nephritis, of whatever form, hemorrhagic, arteriosclerotic or degenerative, is likewise a wholly different disease from what we call "toxemia of pregnancy."

That leaves us only two entities: one, the eclamptic syndrome, which is eclampsia or pre-eclampsia, and the second, about which there has been so much disagreement and which I have called low reserve kidney, and which others have called hypertensive disease, vascular disease, and albuminuria of pregnancy. I do not claim that the term "low reserve kidney" is correct. It is not essential hypertension, it is not chronic nephritis, and certainly it is not eclampsia. Perhaps it may be, as claimed by Kellogg, a very mild form of pre-eclampsia.

Now what Dr. Strauss is talking about is true toxemia. By that I take it he is talking about eclampsia and pre-eclampsia, not about chronic nephritis, not about nephrosis, not about essential hypertension. The water balance in the body is an intricate and delicate mechanism. We have several factors to contend with, such as the serum proteins, the electrolyte balance and the kidney.

I cannot help but feel that something should be said about the recent work on the hormones. Thorn, Nelson and Thorn have reported water retention in normal women at the intermenstrual and premenstrual periods, when the level of sex hormones is high. In dogs water retention has been induced by the administration of estrone, accompanied by increased K excretion. There appears to be enough evidence at present to ascribe to the sex hormones an ability to regulate, in part at least, the excretion of certain of the inorganic ions, Na, K, and Ca, as in the case of the adrenal cortex hormone or hormones.

I do not wish to detract from the importance of the role played by the colloid osmotic pressure, as so well shown by Dr. Strauss. The normal individual compensates for increased Na intake by increased Na excretion, whereas the person with a low colloid osmotic pressure of the blood, responds to such increased Na intake by fluid retention rather than by increased Na excretion. Here then the low osmotic pressure is primary to the balance of the electrolytes. But, in the case of pregnancy, we should also remember that after delivery retained water is very rapidly excreted, a finding which can hardly be explained mainly on the basis of changes in serum protein content, or on differences in Na intake. May this not perhaps be associated with rapid changes in the excretion of inorganic ions, dependent, in part perhaps, upon sex hormone levels in the body?

DR. ALFRED C. BECK.—If Dr. Strauss' deductions are correct, should not the greatest amount of water retention occur early in pregnancy? The most carefully conducted balance studies, including those of Barr and Merlin in the dog, show a negative nitrogen balance or at least a tendency toward the same in the first trimester. All such studies, on the other hand, show a rather marked retention of nitrogen in the latter part of pregnancy. Early in pregnancy, patients are accustomed to take an excess of sodium in the form of sodium bicarbonate. This also should favor water retention in that period.

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## DISCUSSION

DR. ALVIN J. B. TILLMAN.—In discussing the type of toxemia characterized by hypertension, albuminuria, with or without edema which occurs in the last trimester of pregnancy, and is frequently accompanied by headache, visual disturbances, and epigastric pain or distress, I cannot agree with the view that the edema is responsible for the toxemia. It seems to me that a very good case could be made as well for cell volume, plasma volume, serum, or albumin and globulin determinations. Dr. Strauss excludes various other factors as causative agents in the etiology of toxemia, mainly because of the existing confusion in the various fields, but this, in my opinion, is an inadequate reason for exclusion. For example, the fact that endocrinology is in a state of confusion does not rule out the possibility of hormonal imbalance in toxemia. And hypoproteinemia frequently results from the loss of protein through the kidneys, in addition to the factors mentioned by Dr. Strauss.

In the type of toxemia under discussion the first evidence of toxemia very frequently is a slight elevation of blood pressure. The question of body weight as evidence of toxemia of pregnancy seems of importance in a large number of cases, but Sidell and Mack pointed out not very long ago that in a very carefully controlled series of one hundred cases of toxemia they were unable to determine any relationship between the body weight and the severity or type of toxemia. Furthermore, in their control series of six hundred cases nearly 40 per cent also gained a tremendous amount of weight, and any etiologic factor concerned must explain the gain of large amounts of weight in the normal pregnant as well as in the toxic pregnant woman.

If I were to say to you as obstetricians that patients with pre-existing hypertension and pre-existing nephritis who became pregnant have a greater incidence of the same toxemia under discussion you might refute the argument, but if I were to ask you why you take such great care of such patients, and are so cautious about those with hypertension when they are seen early in pregnancy, you would reply that your care is first in the interest of the fetus, to prevent prematurity and fetal death, and second in the interest of the mother. In the latter case your greatest care is to avert, if possible, the appearance of the sudden onset of acute edema, increasing hypertension, albuminuria, headaches, and epigastric pain—in other words, pre-eclampsia. And the probable reason why pre-eclampsia and eclampsia are said to be more infrequent in the presence of pre-existing hypertension and chronic nephritis is because of the care that you take of the patient. This view has been stated by Thiell and Read, and I am in complete agreement with them. It seems to me, therefore, that if hypoproteinemia is responsible, it certainly must occur in the cases of hypertension during pregnancy, and to explain a specific or a water toxemia one must explain the lack of hypoproteinemia in such a situation. Furthermore, I have not infrequently observed pre-eclampsia and eclampsia with normal serum protein with edema. Patients who have had convulsions with all the enumerated symptoms except the edema cannot be ruled out of the group because of that, and dry eclampsia, as stated in the classical textbooks, is the most severe type of eclampsia.

DR. HENRICUS J. STANDER.—Plass and Mathews, in 1926, showed that pregnancy is usually associated with a decrease in the total plasma proteins, amounting to about 9 per cent. Their work has been well corroborated by many other workers,

# THE OBSTETRIC MANAGEMENT OF PATIENTS WITH TOXEMIA\*

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THE management of pregnant patients with toxemia has been a varied one during the past few decades. The medical treatment, entailing dietary regulations, bed rest, the use of bromides, chloral hydrate, barbiturates, or the intramuscular or intravenous injection of magnesium sulphate, has been used extensively in some clinics. In other hospitals the surgical treatment (the early termination of the pregnancy either by accouchement forcé or cesarean section) has been used exclusively. The treatment of choice, namely the obstetric, should be a logical combination of both medical and surgical procedures. Since the efficacy of the treatment used can only be judged by the number of *normal* surviving mothers and babies, we shall discuss our obstetric management of toxemic patients and the results.

The hospital incidence in the United States of noneconvulsive toxemia of pregnancy varies from 0.2 to 29 per cent, average 4 per cent; and the maternal mortality for this condition ranges from 0 to 10 per cent, average 1.7 per cent. Dieckmann states that there are as many and probably more deaths from this condition than there are from eclampsia. The fifteen state mortality study revealed that 26 per cent of the maternal deaths were due to toxemia. Twenty-three per cent of these toxemic deaths occurred in undelivered women of whom 31 per cent belonged to the noneconvulsive group. The Philadelphia report indicates that 29 per cent of the deaths were associated with toxemia and that 19 per cent of the patients died undelivered. Unpublished data of ours indicate that similar figures are true for Chicago.

The uncorrected fetal mortality (abortions, stillbirths, and neonatal deaths) for several series of cases is illustrated in Table I. We have attempted to compare similar data from various articles with our results.

TABLE I

	TOTAL %	PRE-ECLAMPSIA		ESSENTIAL HYPERTENSION		VASCULAR-RENAL DISEASE	
		MILD	SEVERE	MILD	SEVERE	MILD	SEVERE
Peckham	14.9	(9.5)*	17.7			25.5	
Stander	15.8	(8.3)*	18.9			29.0	
Tillman and Watson	25.7		24.0	3.0	30.0	36.0	69.0
Present Report	12.8	6.0	12.0	6.0	21.0	12.0	37.0

\*Fetal mortality for low reserve kidney.

\*Read at a meeting of the Chicago Gynecological Society, January 20, 1939.

Only recently, I had a case of twin pregnancy in which the mother was placed on a milk diet and given cathartics. The edema disappeared, the blood pressure returned to normal and she lost considerable weight. As a result, I was perfectly satisfied from the clinical standpoint but, because of her low plasma proteins, I increased the protein intake considerably. Following this, her blood pressure went up very rapidly and a very marked albuminuria occurred, with the result that I was forced to empty her uterus. I therefore believe Dr. Strauss will find, when he has a larger series, that not all patients will respond as did those reported by him this evening.

DR. GEORGE E. ANDERSON.—Dr. Strauss has considered only a small percentage of cases, representing probably 15 per cent of all cases of so-called toxemia. Probably the majority of toxemic patients are not correctly diagnosed from the internist's point of view, particularly such cases as those with low renal threshold, chronic nephritis and liver disorders.

If I understood Dr. Strauss correctly, he claims not a very marked lack of serum protein, but rather a *relative* lack which in the presence of other factors, will decide the presence or absence of edema. Certainly none of the pregnant women whom we customarily see have serum protein levels anywhere near the critical level of near 5. When you add to the condition of slightly reduced serum proteins, however, one of hypermetabolism and its attendant demand on the maternal protein economy together with the increased protein needs of the growing fetus, the increase of vascular volume and hydrostatic pressure incidental to late pregnancy, even slight changes in serum protein content will produce remarkable effects.

It is certain that Dr. Strauss' patients lost considerable of their body-weight or hidden edema when their serum proteins were increased to normal or close to normal levels. This may not have been due to an absolute increase in serum protein but a relatively increased value through sodium and water depletion. I doubt if we see the average pre-eclamptic woman long enough to treat her sufficiently to raise a low serum protein to a normal level merely through protein feeding. It is conceivable, however, that slight protein deficiency may be corrected or the ill-effects of such slight deficiency be minimized by careful attention to salt and water metabolism.

Studies of the type which Dr. Strauss has presented will eventually lead to a solution of the problem of true eclampsia. There are probably a dozen investigations which should go hand in hand with this consideration of water metabolism. The factor of liver, for example, in water metabolism has not been sufficiently stressed as a factor in toxemia or even in hypertension. We do not know the cause of capillary permeability or of the hypertension which accompanies eclampsia. Dr. Strauss presented just one factor—water retention in eclampsia in relation to salt and plasma proteins.

DR. STRAUSS (closing).—I wish to emphasize that the weight changes observed in these pregnant women occurred without change in the plasma protein level. They were brought about solely by changes in the electrolyte intake, although, as Dr. Anderson has pointed out, it is the plasma protein osmotic pressure level which is the limiting factor involved.

Dr. Stander has raised the question of hormones. They present a fertile field for speculation, almost as mysterious as the now defunct "toxins." Thus far, no one has been able to produce "toxemia of pregnancy" by administering hormones or to relieve it with either hormones or antihormones, whereas both these may be accomplished by altering the water balance.

In conclusion, allow me to state once more that approximately 85 per cent of our series of cases of so-called "toxemia" represent primary vascular or renal disorders in which pregnancy is the complication rather than the cause.

TABLE III. DELIVERY OF FETUSES WEIGHING OVER 1,000 GM.

METHOD	1931-36 %	1936-37 %	1937-38 %	1931-38 TOTAL %
Normal	54	54	57	55
Operative vaginal	(a) 30	34	32	30
Forceps	24 (b)	29	27	25
Dührssen incision	1	1	1	1
Craniotomy	1	1		1
Cesarean section	16	12	11	15
Total Deliveries	899	219	215	1,333

Difference between (a) and the sum of column (b) represents breech extractions and podalic versions.

special value in deliveries before term where there is no disproportion and dilatation stops at 5 to 7 cm. Premature babies are especially susceptible to intracranial injury and after a suitable period of labor without progress, the cervix should be incised and the baby delivered with forceps after an episiotomy. The craniotomies were almost without exception performed on dead fetuses. The number of deliveries by abdominal hysterotomy steadily decreased, but is still too high. We prefer early delivery of the severe pre-eclamptic who is on the verge of eclampsia, and we rupture the membranes if the cervix is "ripe" (meaning that the cervical canal is obliterated and the margins soft and dilatable). If the cervix is not "ripe" and the fetus is estimated to weigh over 2,000 gm., the pregnancy is usually terminated by cesarean section. Patients with essential hypertension or vascular-renal disease, who comprise 12 and 36 per cent, respectively, of our toxemic patients, quite often require delivery at thirty-two to thirty-six weeks' gestation because of the blood pressure or large amount of albumin in the twenty-four-hour urine. At this period of pregnancy the cervix is usually uneffaced, firm, and closed. These patients should also have a tubal ligation. These various reasons, together with a lower fetal mortality, induce us to favor cesarean section.

Immediate delivery by cesarean section, because the toxemia was endangering the patient's life, was deemed necessary in only a small percentage of the cases. Over 20 per cent of the patients delivered by cesarean section had either primary or contributory maternal indications such as contracted pelvis, previous cesarean section, placenta previa, or abruptio placentae. Sterilization by tubal ligation was done for various indications in over 40 per cent of the operations. Approximately 60 per cent of the cesarean sections were performed on patients with vascular-renal disease primarily for two reasons: one, to deliver the baby, which was usually premature, with the least trauma; and the other to permit tubal ligation. Although our total incidence of cesarean section in toxemic patients has decreased, the reduction has been limited to the pre-eclamptic group.

Using criteria described in a previous paper we have classified patients as having pre-eclampsia, essential hypertension, or vascular-renal disease. Data as to the onset of labor and methods of delivery for each group are given in Table IV and illustrate how the diagnosis of the disease influences the management. Thus, if the diagnosis was pre-eclampsia, we

Hess states that 16 per cent of the mothers of their premature fetuses had toxemia and that 26 per cent of these fetuses died.

Clifford reports that at the Boston Lying-in Hospital 30 per cent of their premature fetuses born alive are from toxemic patients and that the mortality is 29 per cent.

Dunham and Tandy state that in 2,000 stillbirths collected from various hospitals, toxemia occurred in 25 per cent of the cases in the period from thirty-two to thirty-five weeks. Theoretically, all babies of this age should survive.

The maternal and fetal mortality of toxemia of pregnancy can be estimated, but we have no means of determining the maternal morbidity (such as vascular-renal disease or permanent injury to the pelvic tissues from forced delivery) or fetal morbidity (prematurity, intracranial hemorrhage, etc.) associated with it.

Table II lists data as to the onset of labor for several consecutive periods and also a column for the total cases. Fractions of a percentage have been dropped for obvious reasons. A medical induction of labor means that labor ensued after injections of pituitrin had been given. If the membranes were artificially ruptured and pituitrin given, the case was included under the former condition. "Operative" includes all cesarean sections, abdominal and vaginal hysterotomies, and a few therapeutic abortions by dilatation and curettage.

TABLE II. ONSET OF LABOR FOR ALL CASES

METHOD	1931-36 %	1936-37 %	1937-38 %	1931-38 TOTAL %
Normal	58	72	73	64
Induced	21	14	13	18
Pituitrin	9	10	10	9
Rupture of membranes	4	3	1	3
Intrauterine bag	6	1	2	5
Intrauterine pack	2			1
Operative	21	14	14	18
Total cases	944	223	222	1,389

An active, perhaps even a surgical, treatment of toxemia is represented by the results for 1931 to 1936. A definite trend to the obstetric management began about 1933 and is represented by the two periods of one year each. The number of patients, who had labor induced or an operative termination of the pregnancy before labor, have each decreased 33 per cent and undoubtedly each could be reduced still further. The intrauterine pack has been discarded and the bag is used only in selected cases. The reason for our change of management has been because the fetal mortality is lower and the maternal results better.

Data as to the delivery of fetuses of 1,000 gm. and more are given in Table III. The number of vaginal operative deliveries is high, but a major portion of these deliveries were in primiparas who were delivered by prophylactic forceps. As a rule, we believe that difficult operative procedures such as Dührssen's incisions are contraindicated in toxemic patients because of the prolonged anesthesia, tendency to shock, and added danger of injury to the baby. However, these incisions are of



Various data as to fetal mortality are given in Table V. There were 1,389 pregnancies and 178 (12.8 per cent) patients had no live baby on discharge from the hospital. Twin pregnancies, both babies living, have been counted as one fetus, but if one was dead, both were considered dead. Our data include all macerated fetuses and spontaneous abortions. We wished to determine what chance a toxemic patient has to obtain a

TABLE V

WEIGHT OF FETUS GM.	TOTAL GROUP			FETAL MORTALITY %		
	NUMBER	%	P. M. %	NORMAL ONSET	INDUCED LABOR	ABDOMINAL LAPAROTOMY
<i>A. Fetal Mortality in Various Weight Groups in Relation to Onset of Labor</i>						
1- 999	45	3	96.0	100.0	100.0	85.0
1,000-1,499	45	3	71.0	84.0	81.0	30.0
1,500-1,999	53	4	28.0	37.0	13.0	32.0
2,000-2,999	401	29	8.0	5.8	9.6	11.4
3,000-3,999	683	51	3.0	1.6	8.8	6.4
4,000	133	10	3.0	2.1	7.4	0.0
Total	1,389		12.8	6.1	15.9	16.7
Number				886.0	251.0	204.0
<i>B. Mortality of Viable Fetuses</i>						
Over 1,000	1,315	98	8.0	5.2	14.3	12.0
Over 1,500	1,270	95	6.0	3.6	9.1	11.0
Over 2,500	1,077	80	3.9	2.5	8.3	6.1
<i>C. Comparison of Fetal Mortality for Three Periods</i>						
1931-1936 Total	944		15.5	7.3	16.6	19.2
Over 1,500 gm.	851	90	6.8	4.5	9.6	12.2
1936-1937 Total	223		7.2	2.5	12.9	7.7
Over 1,500 gm.	213	95	2.3	1.3	3.0	4.0
1937-1938 Total	223		7.2	5.4	14.3	10.7
Over 1,500 gm.	209	94	2.3	2.5	4.1	4.1

living baby. Fractions of a per cent have again been dropped unless the groups were large. Swanson, Turner, and Adair studied all fetal deaths from our hospital, including those from toxemic patients, and reported a fetal mortality for groups comparable to the first three of Table V, Part A, of 100, 73, and 22 per cent which are similar to our figures. The mortality of the viable premature (1,000 to 2,499 gm.) from toxemic mothers is 26 per cent which is higher than the premature mortality of the hospital, 19 per cent. Potter states that the fetal and neonatal mortality for all term infants, which includes babies from toxemic mothers, is 1.9 per cent which is much less than our rate of 3.9 per cent. It is obvious that toxemia is associated with a high fetal and neonatal mortality for both term and premature babies.

The effect on the fetal mortality of a normal onset, of induced labor, or of delivery by abdominal hysterotomy is demonstrated in Part A. It is obvious that patients who had a normal onset of labor were almost invariably of the mild type and that a laparotomy was used almost entirely for the severe cases. Laparotomy seems to offer the best chance for the fetus of 1,000 to 2,000 gm. and those over 4,000 gm. Induction of labor

would favor normal delivery. If the patient had vascular-renal disease or severe essential hypertension, premature delivery and sterilization would usually be advisable. If the patient had a mild essential hypertension, normal delivery would be chosen.

TABLE IV

	PRE-ECLAMPSIA	VASCULAR-RENAL	ESSENTIAL HYPERTENSION
<i>Onset of Labor (Per Cent)</i>			
Normal	70	57	70
Induced	24	24	14
Elective operation	6	18	15
Therapeutic abortion		1	1
<i>Method of Delivery or Termination of the Pregnancy (Per Cent)</i>			
Normal	50	58	50
Operative vaginal	*40	15	34
Forceps	*34	11	26
Operative abdominal	10	27	16
Cesarean section	9	20	13
Hysterotomy	1	7	3
Per cent of all toxemias	47	36	12

\*Difference represents breech extractions, podalic versions, and craniotomies.

The figures for the two tables are not additive. That is, the same 6 per cent of the pre-eclamptic patients who had no labor but were terminated by an elective operation are included in the 10 per cent of the second part of the table. The highest incidence of abdominal delivery occurs in the vascular-renal group.

The interruption, if early in pregnancy, was solely in the interest of the mother, and if after the thirtieth week, in the interest of both mother and fetus. The babies in the vascular-renal group were usually small and a large percentage of the patients were multiparas, hence, the low incidence of forceps deliveries. The high operative termination of pregnancy is due in great part to the large number of hysterotomies on pre-viable fetuses (less than 1,000 gm.) and cesarean sections.

The duration of labor was over eighteen hours in approximately 35 per cent and over twenty-four hours in 25 per cent of all primiparas with toxemia. Twenty-five per cent of the multiparas with toxemia were in labor over twelve hours, 10 per cent over eighteen hours, and 5 per cent over twenty-four hours. These data are at variance with statements that labors in toxemic patients are short and easy. A complicating factor is that a number of the labors were induced and they tend to be longer than normal.

The average morbidity for all the puerperal patients using the British standard is 7.8 per cent. Thirty-two per cent of all toxemic patients were morbid; 9 per cent of the patients had temperatures over 39° C. The increased incidence of fever in toxemic patients is probably the result of the increased vaginal manipulation incidental to the induction of labor and high percentage of abdominal deliveries rather than the result of decreased tissue resistance. Severe toxemia is occasionally accompanied by a hyperpyrexia.

## DISCUSSION

The total fetal and neonatal mortality for the last two periods was decreased 53 per cent. There was a 66 per cent decrease for fetuses weighing over 1,500 gm. Potter analyzed all fetal and neonatal deaths in the hospital and stated that the mother had toxemia in 18 per cent of all deaths. No pathology was found at the autopsy in 55 per cent of these fetuses and infants. These are the babies that should be saved.

Peckham noted a close correlation between the fetal mortality and the height of both systolic and diastolic blood pressure. The fetal mortality was 9 per cent with a systolic pressure less than 149; 11 per cent for 150 to 179; 19 per cent for 180 to 209; and 42 per cent for 210 or more. He also noted that the fetal mortality was 8 per cent with no albuminuria; 10 per cent with 1.9 gm. per cent; 23 per cent with 2 to 4.9 gm. per cent; and 42 per cent with 5 gm. per cent and over.

The fetal and neonatal mortality depends on the severity of the toxemia, the age of the fetus when born, and the type of delivery. Our data for 1936 to 1938 demonstrate a marked reduction in both fetal and maternal mortality. The procedures used are discussed in the following paragraphs.

Clifford reports that if the mother's systolic pressure is 180 or more, 50 per cent of the babies are stillborn. They attempt to prolong the pregnancy of toxemic patients until the fetus weighs at least four pounds, but as soon as the blood pressure reaches the above level and the fetus is estimated to weigh four pounds, the pregnancy is terminated. They believe that the mother delivered of a live four-pound baby will have a greater chance of having a baby to take home with her than she would if they waited for a larger sized baby only to have it delivered stillborn.

Over 60 per cent of the fetal and neonatal mortality in toxemic patients occurred in the fetuses weighing 1,000 to 2,000 gm. Since maternal toxemia has no further effect on the fetus once it is born, the treatment of the mother should be directed to prolonging the pregnancy as long as compatible with her best interests to obtain as old and as heavy a baby as possible. The method of delivery with the lowest mortality should be selected. The age of the fetus is of more importance than its weight. The babies, if born prematurely, are usually more vigorous than their weight would warrant.

Clifford reports that the premature mortality at the Boston Lying-in Hospital was 55 per cent for breech delivery, 54 per cent for cesarean section, 33 per cent for normal vertex, and 15 per cent for low forceps with episiotomy. He ascribes the high mortality in premature babies to the use of analgesic drugs during labor and prolonged anesthesia during delivery. The low mortality for the last group he attributed to the shortening of the second stage by an episiotomy and use of forceps with a resultant reduction of trauma to the head. He notes that if no pre-operative medication is used in cesarean section and if this is done under local anesthesia or a very rapid extraction is performed under short gas

results in a very high mortality. If the patients are properly selected, this death rate can be markedly reduced. If medical treatment can be used with safety until labor begins, the fetal mortality is lowest for babies of 2,000 to 4,000 gm.

Part B lists the fetal mortality for three weight groups. Adair considers all fetuses of 1,000 gm. or more as viable. However, although the 1,000 to 1,499 gm. group comprised only 3 per cent of all fetuses, yet the mortality of 71 per cent materially raised the average mortality. The mortality for fetuses over 1,500 gm., which includes 95 per cent of all babies, is within reason for a normal onset of labor but still far too high for induction of labor or cesarean section. The same may be said for babies over 2,500 gm.

Data in Part C are especially instructive. The staff has remained essentially the same but the comparison for the three periods demonstrates a marked reduction in the total mortality and an even more marked decrease in the rate for fetuses over 1,500 gm. for the last two years. This reduction is due to improved prenatal observation and especially to a better understanding of the indications and necessary conditions for terminating the pregnancy. The decrease in the cesarean mortality is noteworthy and is the result of better technique for the delivery of the fetus and expert treatment in our premature nursery.

The type and severity of the toxemia are illustrated by the following data. Labor was induced or the pregnancy terminated in 26, 21, and 36 per cent of patients with mild pre-eclampsia, essential hypertension, and vascular-renal disease, and 10, 21, and 21 per cent, respectively, of these fetuses were lost. Similar figures for the severe groups are 56, 52, and 67 per cent induced, and 18, 20, and 49 per cent, respectively, of these fetuses lost. Thus, the patient with severe toxemia of pregnancy, especially of the chronic type, is confronted with a poor chance for obtaining a living baby.

We have records of 18 maternal deaths. One of these followed a gall bladder operation three months post partum.

TABLE VI

PRIMARY CAUSE OF DEATH	NUMBER OF CASES WHO DIED WITHIN	
	2 MONTHS POST PARTUM	2 YEARS AFTER DELIVERY
Puerperal infection	3	0
Heart disease and/or anemia	3	1
Uremia	1	6
Cerebral hemorrhage	0	3
	7	10

The total determinable maternal mortality associated with childbirth and toxemia or vascular-renal disease over a period of seven years is 1.3 per cent. Many of these patients had a chronic disease, but the pregnancy usually aggravated the process. Our immediate mortality is 7 or 0.56 per cent of which 4 deaths were presumably preventable. There have been no immediate deaths due to nonconvulsive toxemia during the past five years. This record is the result of a proper study of each patient with toxemia.

indicate that 25 per cent of the pregnancies after eclampsia and 15 per cent after noneconvulsive toxemia terminate as described above. Thus, the patient with toxemia is not only confronted with the possibility of her own death or of permanent vascular-renal damage but her chance of leaving the hospital with a live baby is far less than that of the normal pregnant patient.

The fact that there have been no maternal deaths due to noneconvulsive toxemia since 1932 can be attributed to a more thorough study of every patient, earlier hospitalization, and better preparation for delivery. Intravenous injections of glucose solution, dietary regime, blood transfusions, the use of sedatives, diuretics, etc., have their place in decreasing maternal mortality. Since the premature mortality decreased with advancing age at birth, these various procedures have also reduced the fetal mortality because each additional week of intrauterine life increases the fetal weight and age.

Classifying patients as to degree of severity is always questionable and the tendency after discharge is to minimize the seriousness. However, using criteria previously described we divided our cases as follows:

	MILD	MODERATE	SEVERE	TOTAL
	%	%	%	%
Pre-eclampsia	25.7	15.0	6.7	47.4
Essential hypertension	6.2	3.4	2.4	12.0
Vascular-renal disease	12.5	11.3	12.0	35.8

Over 70 per cent of the patients with noneconvulsive toxemia have only a moderate blood pressure, a small amount of albumin, variable amounts of edema, and no symptoms of headache, dizziness, etc. In other words they are mild cases and although they may become severe, treatment will not influence maternal or fetal mortality unless it is basically sound and includes such items as rest, proper food intake, and especially elimination. This preponderance of patients with mild toxemia explains, in great part, the excellent results attributed by various investigators to a high protein intake, the regulation of water balance, a high vitamin intake, etc. We believe that if a result is to be ascribed to a specific substance or procedure no other type of treatment must be used than the one in question.

The serum protein level of our patients is not in the edema level. The average for the normal pregnant patient is 6.5 gm. per cent, and for the toxemic patient, 6.0 gm. per cent. Furthermore, Dieckmann states that the determined and calculated serum colloid osmotic pressure is within normal limits in the normal pregnant and toxemic patients studied by him and that some other theory must be used to account for the edema. The attempt to feed these patients high protein diets has been unsuccessful because we could not, as a rule, force the patient to take more than 100 gm. per day. Nonprotein nitrogen determinations made on twenty-four-hour urines from patients living at home indicate that they ingest on an average of 60 to 80 gm. of protein per day. Thus, the majority of our patients have an adequate nitrogen intake.

If albumin is found during the prenatal examination, the patient is instructed to save the urine for twenty-four hours, measure it, and bring a

anesthesia, the infant usually breathes and cries spontaneously, in contrast with their previous experience of deeply asphyxiated babies which were difficult, if not impossible, to resuscitate.

The stillbirth and neonatal mortality for all cesarean section fetuses weighing over 1,000 gm. is 7.9 per cent. The section mortality of term babies is 3.3 per cent (neonatal 2 per cent) and of premature babies 4.6 per cent (neonatal 3.3 per cent). The mortality for viable fetuses from toxemic patients delivered by section is 12 per cent which is excessively high. Since the operation is usually performed in the interest of the baby, this high mortality deserves comment. Half of the deaths are in the prematures and yet Potter has found no pathology in a high percentage of these babies with the exception that she has noted that the amount of fluid in and over the meninges is increased.

Robb reports a fetal mortality of 41 per cent for premature infants delivered by cesarean section and suggests the following explanation. The usual technique of extraction of the fetus is rapid and the cord is clamped at once. Thus, the uterus has not been able to squeeze most of the placental blood into the fetus resulting in a loss of blood which may be excessive in premature fetuses. In view of Potter's finding of cerebral edema, we believe that the loss of plasma protein is also of importance. No studies have been made of these fetuses. Barcroft reports that at a period in the goat which corresponds to about thirty weeks in the human gestation, approximately 75 per cent of the blood is in the placenta, while only 25 per cent is in the placenta at term. Thus, the improper delivery of the premature baby would leave a large amount of fetal blood in the placenta. The treatment used by us is to deliver the head of the fetus and produce uterine contractions with an oxytocic and when the uterus contracts, to deliver the body slowly. When the cord has stopped pulsating, its contents are stripped toward the fetus. No drugs are given before operation and over 60 per cent of our cesarean sections are performed with local anesthesia. As soon as the cord is dressed, the premature baby is placed in a Hess incubator.

Since we strive to decrease the fetal mortality in pregnancy toxemia, the question naturally arises as to the future of these babies. No data are available for term infants, but Mohr and Barthelme have made an exhaustive study of 250 of the 987 prematurely born children treated at the Sara Morris Hospital Premature Station. The controls were 152 siblings. They state that from ages one year to seven years inclusive, a sufficient number of examinations have been made to insure reliable conclusions. The physical growth, mental development, habit formation, and social adaptation were analyzed. If those babies having intracranial hemorrhage are omitted, the development of the premature baby from a toxemic mother is similar to that of other prematures and what is most important, similar to that of term babies born of normal mothers. Therefore, if the fetus is born alive and survives, maternal toxemia can have no further influence on its life or development.

Young has reported that the incidence of abortion, premature delivery, stillbirth, and abruptio placentae is 23 per cent in patients who have had toxemia of pregnancy and 10 per cent in normal patients. Our data

stillborn fetuses. We have also been giving these patients 1 to 2 gr. of thyroid per day with the idea of stimulating their metabolism. To date we have seen no ill effects. Our series is too small to warrant any conclusions as to the value of thyroid therapy.

Shute stated that he could stop further separation of the placenta in early cases of abruptio placentae with fresh wheat germ oil. Since this condition occurs frequently in patients with vascular-renal disease, we have been giving such patients vitamin E after the twenty-fourth week. We rarely expect to carry these patients beyond thirty-two to thirty-four weeks because either the blood pressure goes to 200 systolic or more or the albuminuria exceeds 5 gm. per twenty-four hours. In either event we believe the pregnancy should be terminated in the interest of the baby. Shute now states that his results are due to the use of fresh crude wheat germ oil which has been kept cold.

Any increase in the severity of the signs or appearance of the usual premonitory symptoms in the *pre-eclamptic* patient should always suggest that eclampsia may be imminent. Thus, admission to the hospital is imperative and termination of the pregnancy advisable if the systolic pressure reaches 170 or if it increases 50 mm. or more; the urine volume decreases to less than 800 c.c. per twenty-four hours; the albuminuria amounts to more than 5 gm. per twenty-four hours or its concentration is 0.5 per cent; the weight gain has been more than 1.5 pound per week with a sudden increment of two or more pounds per week; the edema becomes marked or if cerebral or visual symptoms appear.

If the patient has *essential hypertension* or *vascular-renal disease*, eclampsia is uncommon, but the danger, especially after thirty weeks, is fetal death in utero because of placental infarction, retroplacental hematoma, or abruptio placentae. These patients are hospitalized and the pregnancy terminated when the systolic blood pressure rises to 190 mm. or more; albuminuria is more than 5 gm. per twenty-four hours; marked edema appears; or the previously described symptoms develop.

Pregnancy is either the cause of the toxemia or a very important exciting factor, and for that reason it must occasionally be terminated. It is the consensus of opinion today that the majority of the toxemias of pregnancy are best treated by medical means until it is possible to terminate the pregnancy by a safe induction of labor. The following outline lists the criteria used for determining the management of the pregnancy. Each case must be individualized. The age, parity, duration of the pregnancy, fertility of the patient (number of years married and time required to conceive), advisability of future pregnancies, and the diagnosis of the condition, i.e., whether it is pre-eclampsia or vascular-renal disease, must be carefully evaluated.

The patient with chronic glomerulonephritis as a rule cannot go through a pregnancy without danger to life and has very little chance of obtaining a living baby. The patient with vascular-renal disease will usually have more evidence of increased damage as indicated by a higher blood pressure, decreased renal function or increased retinal pathology if the pregnancy is permitted to continue.

sample of the mixed twenty-four-hour specimen. The amount of protein is determined by the Esbach method. If there are more than 5 gm. per twenty-four hours the patient is hospitalized. If the patients show edema, gain more than one pound per week, or have a blood pressure of more than 140 systolic, they are placed on a salt poor diet. The twenty-four-hour excretion of sodium chloride must not exceed 3 gm. if the limitation is to be of any value. If the weight gain is still excessive, fats are either curtailed or eliminated from the diet. An unbalanced diet is not used for a period longer than two weeks before delivery is contemplated, and the eclamptic diet which consists of fruits and fruit juices is used for only one week.

The average weight gain according to numerous reports in the literature and our own data is 21 pounds. We believe this is excessive. If at conception the patient's weight is normal, all available data indicate that there is no need for the normal pregnant patient to gain more than the weight of the products of conception and of the physiologic changes associated with pregnancy. The weight of the fetus is comparatively negligible until the last trimester of pregnancy when its weight increases from 1,000 gm. at twenty-eight weeks to 3,400 gm. at term. During this period its requirements for calcium, phosphorus, nitrogen, and iron are maximum. This indicates that the patient's diet for the first six months of pregnancy should be no different from that of the nonpregnant. It may be that the low incidence of toxemia among some native peoples is due to this fact. We have been attempting to obtain data as to weight gains in animals during pregnancy, but here again conditions are artificial and all domestic animals gain weight during pregnancy. Roderick and Harshfield have studied a pregnancy disease of sheep and state that the disease has a mortality of 90 per cent and that 10 to 25 per cent of a flock will die. Important factors are overfeeding and lack of exercise. If the sheep are compelled to walk several blocks for their food, the disease does not occur.

It has been known for many years that patients who have marked albuminuria or marked hypertension usually have very small babies and small placentas. It has always been assumed that the size of the fetus is due to the small placenta. We have noted on a number of occasions that the babies of patients who had been treated for hyperemesis gravidarum with large amounts of intravenous glucose were larger than normal. Furthermore, the babies born of diabetic mothers whose blood sugar level was always high are usually overweight. It seemed that if the fetus had an excess of easily available food (glucose) during the first trimester, it would be larger and thus require a larger placenta. It is highly probable that the size of the early placenta is controlled by the fetus and not vice versa. We have given intravenous injections of 500 c.c. of a 20 per cent glucose solution to a few patients with vascular-renal disease, but in none of them before the middle of pregnancy. We have also suggested to several of these patients when seen early in pregnancy that they attempt to maintain a high blood sugar by constantly eating candy. On several occasions living babies have been obtained in these patients with vascular-renal disease where previously they had had one to three



## CONCLUSIONS

The average maternal mortality in representative hospitals for non-convulsive toxemia of pregnancy is 1.7 per cent. Our mortality for preventable deaths is 0.4 per cent. One-half of our immediate deaths were due to infection and the remainder to heart disease and/or anemia.

Over 13 per cent of our toxemic mothers are discharged without a living baby. Seventy per cent of these deaths occurred in fetuses weighing less than 2,500 gm., but this group comprised only 20 per cent of the series. The fetal mortality for all fetuses weighing over 1,000 gm. was 8.0 per cent; over 1,500 gm., 6 per cent; and over 2,500 gm., 3.9 per cent. Toxemia does cause an increased fetal mortality.

Cesarean section yielded the lowest mortality for fetuses weighing from 1,000 to 1,999 gm. (31 per cent) and over 4,000 gm. (0 per cent). The mortality for viable fetuses was 12.0 per cent.

Normal labor gave the lowest mortality for fetuses weighing 2,000 to 3,999 gm. (3.0 per cent). The mortality for viable fetuses was 5.2 per cent.

Induction of labor gave a high mortality for all weight groups and is now used only in selected cases.

The fetal and neonatal mortality for the first five years was 15.5 per cent and for the last two years has been 7.2 per cent. Similarly the mortality for fetuses weighing over 1,500 gm. was 6.8 per cent for the first period and only 2.3 for the last two years.

Labor should only be induced in suitable cases. That is, there should be no cephalopelvic disproportion, the fetal position should be a normal one, and the cervix should be "ripe" (effaced, soft, and dilatable). Rupture of the membranes and, if contractions have not started at the end of twelve hours, the injection of one or two minims of pitocin at thirty-minute intervals until uterine contractions occur every three or four minutes or until 8 doses have been given is the safest method. Occasionally when rapid delivery seems imperative, a bag may be inserted within the uterus.

Cesarean section should only be used in the pre-eclamptic patient when eclampsia seems imminent and delivery through the vagina seems unwise. It is also indicated in patients with essential hypertension or vascular-renal disease in the interest of the baby if delivery is necessary before term and the cervix is not "ripe." Sterilization as an indication for the operation is unwarranted.

The morbidity for all patients amounts to 7.8 per cent, but for toxemic patients alone, the morbidity is 32 per cent. This high incidence of fever is due primarily to the excessive vaginal manipulation and high operative rate in toxemic patients.

The duration of labor in toxemic patients is longer than normal.

The weight gain in normal pregnancy should amount to the weight of the products of conception and of the physiologic changes associated with pregnancy.

The weight of the fetuses from toxemic patients is as a rule less than the average for the period of pregnancy. These babies are immature

## CRITERIA USED FOR DETERMINING THE MANAGEMENT OF THE PREGNANCY

*Group A*

1. The systolic blood pressure is consistently 160 or more.
2. The albuminuria amounts to more than 5 gm. per day.
3. There is edema of the legs, hands, face, and/or of the vulva.

*Group B*

4. Cerebral, visual, and gastrointestinal symptoms and signs.
5. Hematuria.
6. Oliguria or anuria.
7. Jaundice.
8. Tachycardia of 120 or more per minute.
9. Cardiovascular impairment (edema of the lungs, cyanosis, etc.).
10. Blood nonprotein nitrogen which is more than 50 mg. per cent.
11. Blood concentration as indicated by abnormally high or increasing hemoglobin, cell volume, serum protein concentration, or specific gravity of the blood.

## PREGNANCY

*Before 26 weeks:* Terminate if more than one of the signs of Group A are present or if there is no appreciable improvement after 7 days of adequate treatment or if any of Group B are present.

*27-31 weeks:* No interference before thirty-two weeks' gestation unless one or more of Group B signs develop or those in A increase in degree despite treatment.

*32-40 weeks:* If Group B signs are absent, medical treatment until the cervix is soft and effaced and a medical or mechanical induction of labor will be successful. If Group A signs increase in degree or if any of B appear, the pregnancy should be terminated either by:

1. Rupture of the membranes and/or insertion of a bag, or
2. Cesarean section if the cervix is uneffaced and firm. The environment must be suitable and local anesthesia should be used.

Many obstetricians are of the opinion that the amount of vascular-renal damage parallels the duration of the disease and, therefore, advocate the early termination of pregnancy. Gibberd states, "If a patient with albuminuria is treated carefully over a long period, and induction of labor is performed just soon enough to avoid eclampsia, there is a tendency to regard such treatment as an obstetric triumph made possible by the great clinical acumen of the obstetrician. Actually, it is often a grave obstetric blunder, in that, as a result of the prolonged albuminuria, an incurable chronic nephritis may develop." He, therefore, advises that termination of pregnancy be seriously considered if the albuminuria persists for three weeks. We have recently reported our findings in a group of 340 patients who had two or more pregnancies, the first of which was complicated with toxemia. It is our belief that true eclampsia and pre-eclampsia, irrespective of duration, cause no permanent vascular or renal damage. That if the hypertension, proteinuria, or impaired renal function is still present six months or more post partum or if toxemia recurs in a subsequent pregnancy, the patient has an essential hypertension or vascular-renal disease. These diseases differ only in degree. We believe that the patient either had hypertensive arterial disease before pregnancy or a predisposition to it by inheritance or by physical or mental instability (as in the nervous and high strung) and the pregnancy is the exciting factor. Thus, while our ideas as to etiology differ from those of Gibberd and other obstetricians, yet our treatment is in general in accord with that usually prescribed.

mediate toxemia, would she live long enough to raise that child because of the added damage to herself that we permitted in the waiting? The damage to her hepatic, renal, and vascular systems is even greater if she must undergo the strain of an induced labor. I have lost too many babies by medical or bag induction and hence cesarean section under local anesthesia at the earliest moment consistent with the safety of mother and baby would be my choice in those patients presenting alarming symptoms. I believe also that the sooner an unborn baby is separated from the influence of its toxemic mother, the better its chance for life, no matter how premature, and conversely, the longer it is attached to its toxemic mother the less it is likely to survive even by the method which gives it the best chance for life, viz., cesarean section.

DR. EDWARD ALLEN.—I have analyzed the toxemia cases we have had on the service at the Presbyterian Hospital. Out of 5,722 deliveries there were 357 toxemias of pregnancy. There were 27 fetal deaths; this is an uncorrected fetal mortality. Labors were induced by various methods, some similar to and some different from Dieckmann's. There were 28 cesarean sections which accounted for one fetal and one maternal death. In 32 patients labor was induced by castor oil and quinine aided by separation of the membranes. There were six fetal deaths in this group. Forty-seven of the patients were delivered by castor oil, quinine and bag induction, accounting for seven fetal deaths. Forty-one went into labor after rupture of the membranes which occurred spontaneously in most instances and which probably accounts for the low fetal mortality. Only one infant succumbed in this group. There were 12 therapeutic abortions for toxemia and 13 cases of convulsive toxemia. The uncorrected fetal death rate in our series, therefore, was 7.3 per cent.

I would like to ask Dr. Dieckmann whether he had any tetanic contractions of the uterus following artificial rupture of the membranes and injection of pitocin. We have avoided the use of these oxytocic drugs in the induction of labor, mainly, I think, because in a teaching hospital we have felt that students are a little likely to carry any method we use a little farther than the absolute indications might warrant.

We have not used as a partial indication for cesarean section the need for sterilization as frequently as Dr. Dieckmann has suggested. Neither have we been quite so certain in the early allocation of these patients to their toxemic type. We have been more in favor of sterilization by the vaginal route later in the puerperium when we have additional evidence of the type of toxemia.

DR. DAVID S. HILLIS.—There are two things with regard to the management of a toxemia of pregnancy which must be kept in mind. The first is that every woman with a blood pressure of 140/90 deserves our most careful and accurate attention. An increase to this figure or the appearance of other symptoms, is an indication for hospitalization. It is our opinion that throughout the country the death rate from toxemias is increased because the general practitioner waits for the patient to have some severe symptom or a much elevated blood pressure.

The second point is that it is impossible to decide in an individual case of toxemia hypertension whether or not the patient will have convulsions. A patient may have convulsions with a blood pressure of 140/80. Of course this is not common, but others are frequently admitted to the hospital who have had no convulsions and the blood pressure is found to be 200/140.

DR. JOSEPH B. DELEE.—I will discuss three points. First, I would like to define here again as I have done repeatedly for many years the prophylactic forceps. The prophylactic forceps operation is intended to fulfill two general indications or rather two sets of indications. It is intended to be used when the head of the fetus, in normal labor, comes down to the pelvic floor and just begins to separate the pillars of the levator ani. Then prophylactic forceps is done to avoid two sets of dangers, one for the mother and one for the baby. The set for the mother consists of the prevention of injury to the pelvic floor, the connective tissues, the muscles, the displacement of the rectum and pushing back of the anus, and particularly, the prevention of cystocele. It also prevents the tearing out of the cervix, its dislocation from

rather than premature and are usually much more vigorous than their weight warrants. A high carbohydrate diet during early pregnancy may be of value in producing a larger fetus in patients with vascular-renal disease.

No drugs which depress the respiratory center, such as morphine, hyoscine, ether, paraldehyde, etc., should be used before delivery if the pregnancy is being terminated prematurely. Magnesium sulphate or sodium luminal may be given intramuscularly if convulsions seem imminent. Analgesia may be obtained with intermittent gas anesthesia. Episiotomy is especially indicated in the delivery of the premature baby.

The obstetric management of toxemic patients, meaning the proper use of medical and surgical treatment, results in a lower maternal and fetal mortality. Each case must be individualized.

Prenatal care should be intelligently administered in that abnormalities of weight, blood pressure, and urine must not only be recognized but their importance appreciated and proper treatment instituted. We cannot prevent mild toxemia but the rate of development of severe pre-eclampsia can be retarded and the occurrence of eclampsia forestalled. Treatment must be begun early and if necessary the pregnancy terminated before cerebral and visual symptoms appear, or if the patient has vascular-renal disease, before additional injury to the maternal kidneys and arteries has occurred or the fetus dies in utero.

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#### DISCUSSION

DR. DAVID A. HORNER.—About twelve years ago, Hillis, Lash, Cornell, Fitzgerald and I started a study on the therapy of the convulsive type of toxemia at the Cook County Hospital. We prescribed therapy in such a way that we could compare the various treatments. A suggestion to Dieckmann and Brown would be that they use a similar method in their own service perhaps even to the extent of selecting alternate cases, every other one being kept for control purposes with no special treatment other than the simple salt-free diet and routine of hospitalization.

While Dieckmann gives us nothing new in the line of therapy, we find that the baby appears to be given more importance than heretofore. In my own work, I have felt that carrying a mother until viability of the baby or further toward term was dangerous to her own life. Even though she and her baby survived the im-

# THE PHYSIOLOGY OF HYPERTENSION IN ECLAMPSIA

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**D**URING normal pregnancy there are many circulatory adjustments, and it is remarkable that the maternal blood pressure should maintain its normal level in spite of significant changes of blood volume, blood viscosity, and cardiac output. Sustained arterial hypertension occurs, however, in about 9 per cent of late pregnancies.\* Among this group are recognizable cases of chronic nephritis, essential hypertension, and other hypertensive diseases encountered in nonpregnant individuals. The majority of patients with hypertension, however, belong in the groups known as pre-eclampsia and eclampsia, and it is only with this syndrome that we are concerned in the present discussion. It is extremely uncommon to find a true toxemia of late pregnancy without hypertension. An elevated blood pressure is, in fact, the cardinal and most constant sign, and yet its mechanism has never been satisfactorily elucidated.

It would seem worth while to evaluate the several factors which might be the immediate cause of the hypertension, and to consider particularly the possibility that the hypertension of pregnancy toxemias may be due to the liberation of a pressor substance from the maternal kidney or the placenta.

From the standpoint of hemodynamics, the immediate cause of any rise in the blood pressure must be attributed to one or more of five factors:<sup>1</sup> an increase in the cardiac output, an increase in the ratio of the total blood volume to the capacity of the vascular bed, an increase in the viscosity of the blood, a decrease in the distensibility of the arteries, or an increase of the peripheral resistance.

In pregnancy the dynamics of the whole circulatory system are disturbed by a variety of factors. For instance, the increase in the vascular system of the uterus might act as a low resistance arteriovenous shunt which would tend to lower the total peripheral resistance. That such a shunting effect takes place is suggested by Barcroft's<sup>2</sup> observations on the high oxygen content of the uterine veins during the first half of pregnancy. The similarities between the circulatory changes of pregnancy and those accompanying arteriovenous fistula have been pointed out by Burwell.<sup>3</sup> Such a low resistance shunt would tend to lower the diastolic pressure and increase the pulse pressure. On the other hand, the additional capacity of the circulatory system due to the increase in

\*Hospital incidence: 346 women out of 3,850 consecutive deliveries at the Los Angeles County Hospital maintained a blood pressure at rest exceeding 140 systolic and 90 diastolic.

the bed of connective tissue. As far as the baby is concerned, it prevents congestion of the brain, anoxemia, which all students of the subject have proved is the cause of cerebral hemorrhage, and disturbances of the brain which show up during later life. I do not think there can be any objection to the use of prophylactic forceps in this manner.

The second point is that Dr. Dieckmann did not mention bleeding. I believe bleeding still has an occasional use in eclampsia, especially when convulsions are occurring in great rapidity, and defy the routine treatment. Sometimes even if the pulse is not high or the blood pressure not high it may be useful. Just recently we had a patient at the Lying-in Hospital in which the convulsions were coming every hour almost on the hour. We withdrew 300 c.c. of blood and within an hour and a half she sat up in bed and answered questions. She had only one more convulsion.

One other point: On September 6, I was in Berlin and had a long talk with Professor Stoeckel about eclampsia. He is one of the proponents of immediate delivery. When notified that a woman with fits is on the way to the hospital, he calls his operating room and by the time the ambulance is there he is ready to deliver the woman. On the other hand, at the Charité Hospital the opposite is true. There they carry out conservative treatment. Stoeckel said he was at the meeting in Amsterdam of the International Congress of Obstetricians and Gynecologists where they were about evenly divided on the question of conservatism. I have not read the reports from Amsterdam. Our experience is against cesarean section and rapid delivery. Medical treatment of eclampsia is best.

DR. DIECKMANN (closing).—In reply to Dr. Hillis, I may say the purpose of our paper is to stress the early treatment of toxemia of pregnancy. I believe if one is following these patients himself that he can, with a fair degree of accuracy, make a correct diagnosis as to the type of toxemia. The results as published in this, as well as other papers by us, indicate that the maternal and fetal morbidity and mortality have been better within the past few years as compared to the first period.

We have stressed in our paper that we do not favor the terms conservative and radical. Our operative incidence is still quite high but I believe our results of the past few years indicate a low maternal and fetal mortality. I believe a conservative treatment with a patient showing increasing damage is really radical. Likewise, to immediately terminate the pregnancy in a mild case of pre-eclampsia is radical. I think the obstetric management should be a wise combination of the medical and surgical treatment.

Weinstein and Wickerham: Yeastlike Fungi of the Human Vagina. *Yale J. Biol. & Med.* 10: 553, 1938.

In a study of vaginal secretions of 375 women it was found that 23.3 per cent of the pregnant and 7.3 per cent of nonpregnant women harbored yeastlike organisms; that is, 64 per cent of the nonpregnant group and 56 per cent of the pregnant showed signs of infection of the vagina by these organisms. The absence of noticeable disease of the vagina when yeastlike fungi are present is not necessarily an indication of the nonpathogenicity of the organism but may indicate a resistance on the part of the host. There seems to be strong evidence for the existence of a carrier state with the yeastlike fungi. Studies of the vaginal flora in cases in which yeastlike fungi were present revealed that the Döderlein bacillus can be recovered with great frequency, thus casting doubt on the inference that this organism is an indicator of vaginal health. *Staphylococcus aureus* and *albus*, hemolytic and nonhemolytic streptococci and *Escherichia coli* were also recovered.

J. P. GREENHILL.

Such factors would hardly need to be discussed in detail were it not for the fact that some authors have attributed the hypertension of eclampsia to water retention, or even to the altered blood viscosity. The fact that the hypertension may subside after the establishment of a normal water balance is no proof that water or salt retention alone may be the cause of eclamptic hypertension. The occurrence of a positive water balance and the development of edema do not always result in an elevated blood pressure. Indeed, the most severe cases of eclampsia often have no clinical edema.

Blood pressure measurements on women with eclampsia, made at two-minute intervals during and after the rapid intravenous infusion of glucose-saline (1,000 c.c.) and blood or gum-saline (500 c.c.), show rises which rarely exceed 10 mm. Hg and are only transient. Similarly, the duration and magnitude of the fall of blood pressure following the withdrawal of 500 c.c. of blood during eclampsia are small. Since the spontaneous changes of volume and viscosity in the toxemias are of the same order of magnitude as these induced changes, the observations indicate that neither factor is of any considerable importance in the production of the sustained hypertension.

*Distensibility of the Arterial Tree.*—The only really satisfactory method of determining variations in this factor appears to be by measurements of pulse wave velocity. It has been demonstrated theoretically and experimentally, and confirmed by observations, that there is a roughly linear relationship between pulse wave velocity and arterial blood pressure.<sup>11, 12</sup> We find no reports of investigations designed to tell if this relationship is disturbed in the toxemias of pregnancy. On the other hand, histologic study fails to show organic changes in the muscular coat of vessels during eclampsia; nor is there evidence for any changes in distensibility other than the functional decrease which is the regular accompaniment of a raised diastolic pressure.\*

*Peripheral Resistance.*—No satisfactory measurements of peripheral resistance in pregnant women have been published;<sup>13</sup> nevertheless, we are left with the conclusion that an increased peripheral resistance is the immediate cause of the elevated blood pressure. In this respect the hypertension of pregnancy toxemias is of the same immediate mechanism as that of chronic nephritis and essential hypertension.

That the changes in this resistance are functional rather than organic is suggested by the marked lability of the blood pressure, by the absence of histologic changes in the arteries and by the rapid subsidence of the hypertension in most instances after delivery. This suggestion is further confirmed by experiments in which the administration of sodium nitrite by mouth to a group of women with toxemias of late pregnancy resulted in a greater fall of the blood pressure than that observed in normal pregnancies.<sup>14</sup>

Landis,<sup>15</sup> Ellis and Weiss<sup>16</sup> and others have repeatedly shown that in normal persons and patients with hypertension the bulk of the peripheral resistance is in the arterioles rather than the capillaries, and it is reasonable to consider whether the

\*Such a decreased distensibility resulting from the raised diastolic pressure in eclampsia might well account for the increased pulse pressure observed in that disease.

the vascular bed of the gravid uterus would tend to slow the circulation while the simultaneous increase in the volume of blood would tend to accelerate it. Similarly the decrease in blood viscosity must tend to lower the blood pressure.

Thus we have a variety of contrary phenomena whose existence is almost beyond doubt but the relative magnitudes of whose effects have not been measured adequately. It is significant, however, that the vast majority of women (over 90 per cent) compensate so smoothly for these changes that the resulting alterations in arterial pressure, venous pressure, and pulse rate are below the limits of significance. Undoubtedly the compensatory mechanisms of the vasomotor system are called into play in the redistribution of blood, and vasoconstrictor influences in certain areas of the body may be acting to compensate for the lowered resistance of the gravid uterus. This is suggested by the observation of Kyrieleis and Schroeder<sup>4</sup> that normal pregnancy is accompanied by a narrowing of the retinal arterioles, and also by the finding of decreased capillary flow in the nail beds of most pregnant women.<sup>5</sup> Extensive confirmation of these two findings is therefore desirable.

*Cardiac Output.*—It is generally agreed<sup>6</sup> that the cardiac output during the latter half of normal pregnancy is substantially increased, but no measurements have been found on toxemic patients. Such an increase in circumstances other than pregnancy would be reflected in an increase in the product of pulse rate and pulse pressure. That such pulse rate and pulse pressure changes are not regularly found in pregnancy indicates that the observed rise in cardiac output is closely balanced by one or more of several factors: (1) diminished blood viscosity, (2) an increased distensibility of the arterial tree, (3) an increase in the capacity of the uterine arterial system, or (4) a lowered resistance due to the increased cross-sectional area of the uterine blood vessels. Since increased cardiac output in man is almost invariably associated with a normal or lowered diastolic pressure, the rise of diastolic pressure in eclampsia indicates that a further augmentation of the cardiac output is not the immediate cause of the hypertension in this disease.

*Blood Viscosity and Blood Volume.*—The effective viscosity of the blood varies with the blood pressure and the diameter of the smaller blood vessels<sup>7</sup> and, therefore, has not been measured in man. The in vitro viscosity of the blood, however, varies roughly with the concentration of the red blood cells. Changes in the blood volume or in the specific gravity are rarely, if ever, the cause of sustained hypertension. In polycythemia vera, where both factors may undergo a marked increase, the blood pressure usually maintains its normal levels.<sup>8</sup> In normal pregnancy there is a hydremia often resulting in a 10 per cent increase in the blood volume,<sup>9</sup> and in pre-eclampsia this change is exaggerated,<sup>10</sup> but inasmuch as the increased volume is always accompanied by a blood dilution, the viscosity is decreased. The effect of the one change upon the blood pressure would therefore tend to counteract the effect of the other. This same reciprocal action would also hold true during the acute stage of eclampsia when, as Dieckmann<sup>10</sup> has shown, there may be a rather sudden concentration of the blood.



*The Source of the Vascular Toxin.*—The full syndrome of pre-eclampsia or eclampsia with the characteristic histologic lesions of the viscera is not observed in the male nor in the nonpregnant female; therefore it is obvious that the products of conception are in some way concerned with the production of this vascular damage. Such a statement is essentially a truism, and yet its full significance has been ignored by some investigators who either evade the question or state that pregnant women develop eclampsia because they "react differently" to such diseases as glomerulonephritis, essential hypertension, hyperpituitarism, hypothyroidism, hypercholesteremia, urinary back pressure, intestinal stasis, pyelonephritis, salt retention, abscessed teeth, and so on. Any one of these conditions might predispose to the development of eclampsia, but the mechanism of such an effect is at present unknown.

Several authors have ascribed eclampsia to the action of some metabolite of the fetus itself, or to the interaction of fetal and maternal blood. In a previous communication,<sup>26</sup> attention was called to the fact that the toxemias of late pregnancy are several times more common in cases of hydatidiform moles than in normal pregnancies, and it was suggested that this fact might be related to the volume and activity of chorionic tissue. Eclampsia itself has been reported many times with moles. Not only is the fetus eliminated as a source of the vasotoxic factor in such cases, but the placenta is definitely implicated.

The studies of Bartholomew and Calvin<sup>27</sup> and others seem to show beyond reasonable doubt that there is a positive correlation between placental infarcts and eclamp-togenic toxemias, although the question whether such vascular changes are of primary or secondary importance has not been settled. The suggestion that autolytic products arising from these degenerative areas have both toxic and pressor activities is intriguing, but awaits proof. Such degenerative changes would undoubtedly reduce the secretory powers of a placenta, whereas the work of the Smiths<sup>28</sup> regarding the increased chorionic gonadotropic hormone content in toxemic placentas would seem to indicate an increased secretory function in eclampsia. In either case the placenta is further implicated, and it is most reasonable to postulate that placental activity is directly responsible for the development of toxic properties in the maternal blood.

At this point we may well inquire into the relationship which this toxic factor bears to the production of an increased peripheral resistance. There are four possibilities: (1) The vascular toxin may sensitize blood vessels to the action of normally present nervous or hormonal vasoconstrictor influences (e.g., sensitization to pitressin by estrogens); (2) it may synergize (i.e., activate or potentiate) the action of a normally present pressor substance (e.g., renin, postpituitary principle); (3) it may stimulate the production of increased nervous or chemical pressor activity by another organ (e.g., by initiating a renal hypertension); or (4) it may itself be a pressor substance. All such possibilities must be borne in mind during the course of investigations on the etiology of the toxemias of late pregnancy.

*Vasomotor Influences.*—Vasoconstrictor nerve impulses as a cause of the arteriolar spasm cannot be eliminated with any degree of certainty. The vasomotor centers are known to be directly and reflexly stimulated

same may hold true for the hypertension of pregnancy toxemias. An attempt in four cases of eclampsia to confirm the findings of Nevermann<sup>5</sup> regarding capillary spasm—as indicated by a cessation of flow—was unsuccessful in that these four patients showed no recognizable differences from ten male interns with respect to blood flow or morphology of the capillaries of their nail beds. A prolonged stopping of capillary blood flow, rather than being due to capillary “spasm,” is in fact more commonly due to arteriolar constriction.

While studies of the capillary pressure<sup>17</sup> have shown high readings in some cases of more severe eclampsia, this sheds no light on the question of the resistance offered by the capillaries. Owing to our lack of information on this point it is difficult to eliminate the capillary bed as the source of the raised resistance, although from both a physiologic and anatomic standpoint the arterioles are the probable structures responsible. Indeed, Wagener<sup>18</sup> and a number of others have actually observed the diminished diameter of the retinal arteries in the toxemias of late pregnancy.

Since it seems very likely that the proximate cause of the hypertension of eclamptogenic toxemias is a diffuse functional arteriolar constriction,<sup>✓</sup> it is necessary to consider the known causes of increased arterial tonus.

The direct effect of temperature changes upon arterial tonus<sup>19, 20</sup> may be eliminated from our consideration. It would seem that for such a phenomenon to become sufficiently generalized to alter the blood pressure measurably, the temperature of the whole body would need to be reduced far below the usual clinical limits.

There remain two causes of vasoconstriction—vasomotor changes and <sup>✓</sup>direct chemical excitation of the arteriolar muscle. The decision as to which of these two factors plays the predominant role is one of the important unsolved problems remaining in the study of eclampsia.

Before discussing the question of nervous versus chemical influences, it is necessary to divert attention to the anatomic findings in the eclamptogenic toxemias.

*A Circulating Vascular Toxin.*—It has been repeatedly noted that the most constant and probably the most significant lesions of eclampsia are vascular in nature.<sup>21</sup> Even the mild grades of pre-eclamptic toxemias may show glomerular changes when connective tissue stains are used, and there is evidence that such capillary injury is often of a permanent nature.<sup>22</sup> Damage to retinal vessels may be readily demonstrated.<sup>18</sup> The smaller blood vessels of the placenta<sup>23</sup> and of the liver<sup>24</sup> show similar changes. It is quite possible that such vascular injury may give rise to the multiple small thromboses, to the edema of all organs and to the visceral hemorrhages which so commonly accompany eclampsia. Such vascular lesions bear little relation to the degree or the duration of the hypertension; they are not, therefore, secondary to the hypertension, nor necessarily comparable to the vascular lesions observed in experimental malignant hypertension.<sup>25</sup> The only postulate which is tenable is the age-old concept of a circulating “toxin.” Whether this consists of the presence (or absence) of a chemical substance in the blood or a physical alteration of the blood is not known.

The remainder of our discussion is, therefore, based on the assumption that such a change in the blood of eclampsia does exist, and for the sake of convenience—realizing the dangers of applying any term to an unknown factor—we will refer to this as the “vascular toxin.”

present even in the absence of albuminuria. The possibility that such renal changes may effect hypertension through the autonomic nervous system has not been excluded.

*Pressor Substances.*—Since there is not enough evidence to assign the hypertension of eclampsia to the nervous system, the remaining alternative explanation that a direct chemical excitation of the vessel walls is responsible for the increased peripheral resistance should now be considered.

The search for a pressor substance in the blood of eclamptic women has led to repeated failures. Metabolic products of the fetus or placenta, or autolytic products of placental infarcts have been incriminated without proof. Pressor tests of extracts or dialysates of eclamptic blood and spinal fluid on animals have led to negative results.<sup>40</sup> The hope raised by Anselmino and Hoffmann<sup>41</sup> by their alleged discovery of excessive postpituitary principle in the blood of patients with toxemias of pregnancy has been destroyed by the negative results of several workers.<sup>42-46</sup> Repeated and careful quantitative studies of the blood chemistry in the toxemias<sup>47, 48</sup> have failed to disclose the retention of any known substances in amounts sufficient to produce a hypertension.

Significant quantities of circulatory pressor substances might be demonstrable by the transfusion of adequate amounts of blood from toxemic patients to normal pregnant women. Such experiments in which amounts of 400 c.c. of blood were transfused failed to produce any increase of blood pressure in the recipients.<sup>46</sup> Are such failures to demonstrate a pressor substance in eclamptic blood sufficient proof of its nonexistence, or do they merely reflect the inadequacy of our methods?

A similar question is facing the investigators of experimental renal hypertension. The well-known experiments of Goldblatt and his associates<sup>49</sup> showing that a limitation of arterial blood supply to the kidneys results in permanent hypertension, was followed by demonstrations that such hypertension is not abolished by total sympathectomy, renal denervation, transplantation of the ischemic kidney or even pithing of an animal. The deduction was made, therefore, that the kidney, in response to the diminished blood supply, elaborates a pressor substance. A substance (renin) with marked pressor activity may, in fact, be extracted from renal cortex<sup>50</sup> and even subjected to quantitative assay.<sup>50</sup>

In spite of the fact that the presence of a circulating pressor substance in experimental hypertension is widely accepted, Collins and Hoffbauer<sup>51</sup> transferred large amounts of blood from dogs with renal hypertension to normal dogs without observing a rise of blood pressure in the recipients. Similarly, Pickering<sup>52</sup> and others have transfused normal human beings with blood from patients with malignant hypertension without observing a rise in blood pressure. By corollary, therefore, the failure to obtain a rise of blood pressure in human recipients of eclamptic blood does not eliminate the possibility of a circulating pressor substance.

More direct evidence for the existence of a circulating pressor substance is suggested by the report of Allen and Adson<sup>53</sup> of a woman who had a sympathectomy extensive enough to lower a previous hypertension

by slight changes in the pH or in the carbon dioxide content of the blood, such as may occur in eclampsia. Reflex stimulation of the centers, such as occurs with pain, with the immersion of a hand into ice water (the "cold test"<sup>29</sup>) or even with psychic stimuli, may produce hypertension of varying degree in both normal and eclamptic patients. One may frequently observe, for example, the onset of convulsions and an abrupt rise of the blood pressure following a sensory or psychic stimulus to an eclamptic patient.

It must be remembered, however, that the presence of a chemical pressor substance does not necessarily preclude the superimposition of pressor or depressor effects by the nervous system, or vice versa. The problem, therefore, is the assessment of the relative importance of these two factors.

It has been repeatedly suggested that a hyperactivity of the vasomotor centers is associated with an increased sensitivity to the "cold test,"<sup>29</sup> or with an exaggerated rise of blood pressure under emotional stress,<sup>30</sup> or with a hypertensive personality make-up as found by Ayman<sup>31</sup> in his study of essential hypertension. The blood pressure responses of both normal and hypertensive pregnant women to the "cold test,"<sup>32-34</sup> and to a standardized emotional stimulus have been investigated.<sup>14</sup> (An analysis of our own data and a discussion of their interpretation is beyond the scope of this paper and will be presented in a separate note.) There appears to be a correlation between the degree of response to a sensory and a psychic stimulus, and though such responses seem to be exaggerated in those women who have essential hypertension in pregnancy, there is no significant difference between the responses of women with normal pregnancies and those with pre-eclampsia or eclampsia. The personality make-up of women with toxemias of late pregnancy has also been investigated<sup>35</sup> with similar conclusions.

These observations lend no support to the view that there is a hyper-reactivity of the vasomotor centers in the toxemias of late pregnancy, although it must be pointed out that there is still no unanimity of opinion regarding the interpretation of such vascular reactions.

Pickering,<sup>36</sup> and Prinzmetal and Wilson<sup>37</sup> have evaluated the role of the vasomotor centers in essential hypertension by studying the changes of peripheral blood flow after nerve blocks which eliminate the vasomotor influences, and conclude that there is a humoral mechanism for the increased peripheral resistance. Similar studies have not been applied to the toxemias of late pregnancy. Bearing in mind the similarities between malignant hypertension and eclampsia, the possibility that the mechanism of the raised blood pressure in both these diseases, as well as in chronic nephritis, is similar, will be discussed presently.

*Nervous Reflex from the Kidney.*—In experimental oxalate nephritis<sup>38</sup> and in human acute nephritis,<sup>39</sup> the hypertension is allegedly due largely to a stimulation of the vasomotor centers through the afferent nerves of the kidney. Glomerular lesions of some degree almost invariably accompany the toxemias of late pregnancy, and in the mild grades of toxemias may be the only significant lesions demonstrable.<sup>22</sup> These changes are sometimes observed only after the use of special stains, but they may be

observed in the eclamptogenic toxemias. From a physiologic standpoint, the immediate cause of this hypertension is a functional and diffuse arteriolar constriction.

An increased activity of the vasomotor centers by direct or reflex stimulation cannot be eliminated as a cause of this increased peripheral resistance, but in eclampsia these centers are not abnormally sensitive to psychic or thermal stimuli.

The vascular pathology of eclampsia requires the postulate of a circulating factor which behaves as a vascular toxin. Chorionic tissue is probably responsible for this factor, and the stimulus for its production may be an inadequacy of maternal blood supply to the placenta.

This vascular toxin might produce hypertension in one of several ways: It may act directly as a pressor agent or accentuate the action of other known pressor agents. It is known to produce glomerular damage in the eclamptogenic toxemias. This renal damage may influence the vasomotor centers reflexly, or the resulting reduction of blood supply to the kidney may give rise to hypertension through the mechanism of renal ischemia. The available experimental evidence bearing on such hypotheses is discussed.

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but who nevertheless developed later a transient hypertension in pregnancy. The interesting—though inadequately confirmed—observations of elevated blood pressures in the infants born of toxemic mothers<sup>54</sup> suggest the presence of a diffusible pressor substance in the maternal blood.

*Pressor Substances from the Kidney.*—At this point we are led to the consideration of certain hypotheses which await investigation.

It has already been mentioned that a vascular toxin originating in the placenta might cause sufficient renal injury to stimulate the vasoconstrictor centers through the renal afferent nerves.

Considering our discussion above, a more logical postulate is as follows:<sup>22</sup> The same factor producing the vascular damage and resulting in a thickened glomerular capillary wall results in a “throttling” of the blood supply to the entire kidney. In response to this lessened blood supply, the kidney elaborates a pressor substance which results in hypertension. In support of this theory is the recent work of Dill and Erickson<sup>55</sup> who have been able to produce a syndrome like that of human eclampsia by partially constricting the renal arteries of pregnant dogs and rabbits. The major objection to the theory is its failure to account for the differences observed between the effects of renal ischemia in gravid and nongravid animals or humans or to explain when and why such a reduction of the renal blood supply might occur.

The first objection—namely, the unexplained difference in the reactions of pregnant and nonpregnant animals—might be obviated if the placenta were capable of producing substances which potentiated the action of the renal pressor substance.

This leads us to the crucial question, in what circumstances might the placenta elaborate a potentiator of renin, a vascular toxin or even a pressor substance?

*Pressor Substances from the Placenta.*—It is well known that the blood supply to any organ is largely determined by its metabolic needs. Inasmuch as there are no nervous connections between the maternal organism and the placenta, the only means by which the latter could per se increase its supply of maternal blood would be by causing a maternal hypertension through a chemical mechanism. The possibility has been suggested<sup>26</sup> that the placenta elaborates such a factor in response to an inadequate blood supply, and it has been pointed out how this hypothesis may be correlated with known predisposing causes of eclampsia, such as primiparity, multiple pregnancy, hydramnios, hypoplastic genitalia and hydatidiform moles.

Which of these mechanisms accounts for the hypertension of the eclamptogenic toxemias awaits further investigation. We are not attempting to explain the entire etiology of eclampsia nor to advocate any single theory, but to point out certain physiologic facts and deductions which we hope may serve to clarify the pathologic physiology of the vascular system in the toxemias of late pregnancy.

#### SUMMARY

Changes in cardiac output, blood volume, blood viscosity or widespread organic arterial changes do not account for the hypertension

Depending on the degree of deficiency of this principle, it may possibly be manifested in the blood picture of either the mother or infant, or both.<sup>5</sup>

Frequently there is found a reduction in gastric acidity during pregnancy, and this association with anemia is well recognized. Wintrobe et al.<sup>5</sup> have raised the question as to the presence of antianemic principle in the fetus and its possible relationship to anemia in the infant. As deficiency of the extrinsic factor can produce macrocytic anemia of pregnancy, with transfer of either little or none of this factor to the fetus, absence or diminution of intrinsic factor in the infant may be of considerable importance in producing or aggravating anemia in the newborn.

Because of the rarity of concomitant studies of the blood of newborn infants and their mothers suffering from macrocytic anemia of pregnancy, we are herewith reporting such a study.

Mrs. K., in 1930, when 18 years of age, had her first pregnancy which was normal except for ankle edema. During her second pregnancy she was admitted to Jefferson Hospital, in 1932, because of "low reserve kidney condition and high blood pressure." After three days, she signed her release and was delivered later at home on March 11, 1932, of a seven months' fetus, which died Aug. 11, 1932. The cause of death was ascribed to "enteritis (bacterial origin), lumbar abscess, bronchopneumonia and athrepsia." On Oct. 30, 1933, when six months pregnant, she was admitted to the Misericordia Hospital, because of edema of eight days' duration, elevated blood pressure, vertigo and headache. The onset of symptoms was sudden and spectacular. Studies on admission revealed hemoglobin 15 per cent; red blood cells, 1,100,000; white blood cells, 8,700; polymorphonuclears, 85 per cent, and lymphocytes, 15 per cent. Urea nitrogen 18 mg.; nonprotein nitrogen, 29 mg.; chlorides, 487 mg. On Nov. 3, 1933, the urea nitrogen was 32 mg.; creatinine, 1.1 mg. A transfusion of 100 c.c. of blood was given on Nov. 5, 1933, and 500 c.c. of blood was given on Nov. 7, 1933. On November 6, urea nitrogen was 26 mg.; blood sugar 85 mg. Urea clearance test, Nov. 7, 1933: first specimen, 79 per cent; second specimen, 59 per cent.

*Reticulocyte Count:* Nov. 8, 1933, 10 per cent.

*Gastric Analysis:* November 9, 1933.

	<i>F.</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>
Free HCl	0	0	0	0	6	18	24	18	16
Total acidity	10	10	12	8	16	36	38	36	34

*Reticulocyte Count:* November 14, 1933, 19 per cent.

Blood count on Nov. 24, 1933, was: Red blood cells, 3,000,000; white blood cells, 11,300; hemoglobin, 46 per cent; polymorphonuclears, 78 per cent; lymphocytes, 20 per cent; monocytes, 2 per cent. Platelet count on Nov. 26, 1933, was 420,000.

Patient was discharged on Nov. 26, 1933. She was readmitted on Jan. 7, 1934, and delivered of a normal living female infant and was discharged on Jan. 17, 1934. During this confinement, specific gravity of urines ranged from 1.010 to 1.014. On Jan. 8, 1934, hemoglobin was 57 per cent; red blood cells, 3,000,000; white blood cells, 12,300; polymorphonuclears, 66 per cent; lymphocytes, 8 per cent; monocytes, 2 per cent; rod nuclears, 24 per cent, anisocytosis, poikilocytosis. On January 17, color index was 1.06. On March 16, 1934, patient was examined in postnatal clinic, when she complained of generalized weakness. Blood pressure was 110/70. She was referred to medical clinic, but made no response to follow-up cards.

On Sept. 20, 1934, she was admitted to Philadelphia General Hospital, service of Dr. P. Williams, because of a miscarriage. Her previous menses started June 17, 1934, and was of three days' duration. She claimed that on September 19, after lifting a heavy object, she experienced abdominal pain and passed several clots, followed by continuous bleeding. She had palpitation since her previous confinement,

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## MACROCYTIC ANEMIA OF PREGNANCY AND ANEMIA OF THE NEWBORN\*

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THE relationship between anemia of the newborn and the hematologic picture in the mother has not been studied so extensively as have the anemias of these per se. In fact, the opinion is general that if such a relationship exists, it is only a slight one. Josephs<sup>1</sup> has stated, "We know very little of the factors regulating the formation and destruction of blood, and to what extent these processes in the fetus are influenced by factors derived from the mother. Probably not to any great extent, for anemia in the mother is only exceptionally attended by anemia in the newborn, and the makeup of fetal blood is so different from that of the mother that one must assume a largely independent mechanism." Anemia in the infant may depend upon an insufficient storage of iron in the liver or upon a deficiency of one or more extrinsic factors in the maternal diet.

There is a paucity of information on the relationship between macrocytic anemia of pregnancy and the blood picture of the newborn. A few divergent observations of infants' blood have been reported. If the infant comes to term the blood picture may be normal even though the mother has not received treatment during pregnancy.<sup>2</sup> It may be normal if the mother has been treated with antipernicious anemia principle, blood transfusion or vitamin B complex.<sup>3</sup> Apparently the status of the infant, both as to life and normality of its peripheral blood, depends mostly upon adequate treatment of the mother during pregnancy. One may infer that the factor producing macrocytic anemia in pregnancy may in some manner have a like effect on fetal hemopoiesis. The blood of the fetus has been shown to resemble the blood picture seen in pernicious anemia in response to effective antianemic principle.<sup>4</sup> The antianemic principle is supposedly derived by the interaction of an "extrinsic factor" in the diet and an "intrinsic factor" in the secretion of the stomach.

\*Read (by invitation) at a meeting of the Obstetrical Society of Philadelphia, January 5, 1939.



TABLE I. Mrs. K.

DATE, 1936	HEMOGLOBIN %	MHS R.B.C. C.M.M.	W.B.C. C.M.M.	MYELOCYTES	JUVENILES	STABS	SEGMENTERS	TOTAL NEUTROPHILES	LYMPHOBLASTS	LARGE LYMPHOCYTES	INTERMEDIATE LYMPHO- CYTES	SMALL LYMPHOCYTES	TOTAL LYMPHOCYTES	MONOCYTES	EOSINOPHILES	BASOPHILES	LIVER EXTRACT C.C.	TRANSFUSION. BLOOD	C.C.	ERYTHROBLASTS	POLYCHROMATOPHILIA	MACROCYTES	RETICULOCYTES	PLATELETS, THOUSANDS	VOLUME INDEX
2/16	20	0.74	14,000	0	0	22	58	80	0	6	0	14	20	0	0	0	2	550	+	+	+	+	+	1.85	
2/17	20	0.84	24,700	0	0	64	26	90	0	2	0	6	8	2	0	0	0	450	0	0	0	0	0	60	1.27
2/17	20	0.89	19,200	0	0	20	60	80	2	0	0	18	20	0	0	0	2	350	0	0	0	0	0	1.0	1.28
2/18	25	1.01	11,350	0	0	8	68	76	0	0	0	20	20	2	0	0	2		0	0	0	0	0	1.0	
2/19	30	1.30	16,200	0	0	42	44	86	0	2	0	8	10	4	0	0	2		0	0	0	0	0	1.0	
2/20	30	1.13	12,850	0	0	40	40	80	0	0	0	20	20	0	0	0	2		0	0	0	0	0	1.0	
2/21	30	1.16	16,700	0	0	10	30	40	0	0	0	40	40	20	0	0	4		0	0	0	0	0	1.0	
2/24	30	1.19	10,300	0	0	20	32	52	0	2	0	42	44	4	0	0	4		0	0	0	0	0	1.0	
2/25	30	1.39	11,800	0	3	9	30	42	0	6	0	34	40	18	0	0	4		0	0	0	0	0	1.0	
2/26	40	1.99	9,300	0	0	32	32	64	0	6	0	26	32	4	0	0	4		0	0	0	0	0	3.6	
2/28	40	1.98	12,400	0	0	36	30	66	0	2	0	28	30	4	0	0	4		0	0	0	0	0	3.0	
3/2	51	2.22	14,300	0	0	26	34	60	0	8	0	20	28	12	0	0	3		0	0	0	0	0	1.2	
3/5	53	2.53	19,300	0	0	42	42	84	0	0	0	10	10	6	0	0	3		0	0	0	0	0	2.2	
3/13	55	2.55	8,300	0	0	26	40	66	0	0	0	24	30	2	2	0	3		0	0	0	0	0	1.2	
3/26	45	2.24	10,900	0	0	50	36	86	0	0	0	4	4	6	4	0	3		0	0	0	0	0	2.0	
4/8	52	2.47	8,800	0	0	36	44	80	0	2	0	10	12	8	0	0	6		0	0	0	0	0	1.0	
5/4	25	1.10	8,800	0	0	32	52	84	0	0	0	14	14	2	0	0	3		0	0	0	0	0	1.0	
5/7	25	1.00	9,000	0	0	26	38	64	0	4	0	24	28	4	4	0	6		0	0	0	0	0	1.0	
5/8	25	1.03	19,000	0	2	34	28	64	0	0	0	28	30	4	2	0	3		0	0	0	0	0	2.5	
5/12	25	1.16	24,800	0	0	28	32	60	0	6	0	32	38	2	0	0	10		500	+	+	+	+	5.0	
5/14	35	1.84	16,000	0	0	46	40	86	0	0	0	10	10	4	0	0	10		550	+	+	+	+	4.5	
5/16	35	1.87	27,500	0	0	42	36	80	0	6	0	10	16	4	0	0	10			+	+	+	+	2.6	
5/18	40	2.15	22,000	0	2	30	38	68	0	8	2	22	32	4	0	0	6			+	+	+	+	2.0	
5/28	75	3.15	10,700	0	0	28	38	66	0	4	0	28	30	0	0	0	6			+	+	+	+	1.0	
9/23	75	3.17	13,800	0	0	36	32	68	0	4	2	14	20	4	4	4	3			+	+	+	+	1.0	

and complained of recent hematemesis and a persistent cough since June, 1934. The preceding two months, she had had occasional nocturia with increased frequency. On admission, she seemed well nourished, but pale, with no dyspnea, jaundice or edema. Her cough was moist and nonproductive and there was slight cyanosis of lips. An occasional râle was heard on inspiration over left base. A systolic murmur could be heard at both the aortic and mitral areas, but no cardiac enlargement was elicited. The admission diagnosis was incomplete abortion with sinusitis and bronchiectasis. Blood count on Sept. 22, 1934: red blood cells, 1,705,000; hemoglobin, 35 per cent; white blood cells, 13,800; polymorphonuclears, 66 per cent; lymphocytes, 28 per cent; monocytes, 6 per cent. On Sept. 23, 1934, she was given 300 c.c. of citrated blood. The placenta was passed the same morning. Blood count on Sept. 25, 1934: hemoglobin, 40 per cent; red blood cells, 1,490,000; white blood cells, 32,000; polymorphonuclears, 67 per cent; lymphocytes, 30 per cent; monocytes, 2 per cent; eosinophiles, 1 per cent. No achromia, marked anisocytosis and polychromatophilia. Nucleated reds and high color index. It was thought that she had either a pernicious-like anemia of pregnancy or pernicious anemia. On September 26, she was given 300 c.c. of citrated blood and on September 27, 100 c.c. of citrated blood. She was discharged on Sept. 29, 1934.

On Feb. 7, 1936, the patient, six-months pregnant, was readmitted to the Prenatal Clinic of the Philadelphia General Hospital. She complained of frequent colds and persistent vomiting since the onset of pregnancy, and sudden dyspnea, palpitation and increasing weakness of one week's duration. Her diet excluded fruit juices and meat. Milk and vegetables were regurgitated. Because of the symptoms and marked pallor, macrocytic anemia of pregnancy was suspected and admission to the hospital was advised. On Feb. 14, 1936, she was admitted to the obstetric service of Dr. John A. McGlinn. Examination revealed a pallid, fairly well nourished, white female, aged 23 years, who did not appear acutely ill. No cyanosis was discerned. Sclerae were bluish and palpebral conjunctivae and buccal mucous membranes were quite pale. Venous pulsations in the neck were evident and systolic "bruit" was audible over the great vessels of the neck. The lungs were essentially negative to auscultation and percussion. Slight cardiac enlargement was present and a high pitched systolic murmur could be heard over the pulmonic and aortic areas. A loud, rough, systolic murmur and a soft diastolic murmur were heard over the mitral area. Blood pressure was 120/45. Pretibial edema was noted. The liver and spleen were not palpated. The uterus was definitely enlarged and reached the transumbilical level. She had vomiting and diarrhea on admission. Icterus index was 7. Red blood count on Feb. 16, 1936, was 740,000. Although 550 c.c. of citrated blood, diluted with 100 c.c. of saline, was slowly administered intravenously over a period of one hour and twenty minutes, she experienced immediate reaction with chills, dyspnea and cyanosis, with subsequent rise in temperature to 105.5° F. She responded to symptomatic treatment, but her condition was rather precarious. The next day, February 17, the diarrhea and vomiting had ceased, gallop rhythm was elicited and the left cardiac border extended to the anterior axillary line. Blood pressure was 115/40. A transfusion at 10 P.M. on Feb. 17, 1936, was followed, an hour later, by a reaction characterized by a sense of sternal constriction and a dry distressing cough with wheezing. This reaction was partially relieved by symptomatic treatment.

A transfusion at 8 P.M. on Feb. 19, 1936, was stopped because of an immediate reaction similar to that of Feb. 17, but accompanied by vomiting. The liver and spleen were palpable. Retinal hemorrhages were found scattered throughout both fundi. Improvement was slow but steady. The gastric analysis revealed:

	FASTING	10 MIN.	20 MIN.	30 MIN.	40 MIN.	50 MIN.	60 MIN.
Free HCl	0	15	17	21	0	0	0
Total HCl	20	26	31	40	24	22	20

On March 5, 1936, her clinical improvement appeared so satisfactory that she was discharged the next day. In subsequent clinic check-up, her weight increased from 123½ pounds on March 13 to 138¾ pounds on May 1. Ankle edema persisted and vomiting was a conspicuous symptom. She was re-admitted to the Obstetrical Divi-

sion May 2, with a history of a severe cough of three weeks' duration. Examination revealed her chest to be full of rhonchi, ankles were severely edematous and mucous membranes and nailbeds were very pale. Liver and spleen were not palpable and fetal heart sounds could not be heard. Her red blood count was slightly above 1,000,000 per c.mm. Liver extract was started but transfusion was deemed necessary. Transfusions on May 12 and 14 were followed by severe reactions. Following a spontaneous rupture of the membranes and preceded by a few pains, a precipitous delivery occurred in bed on May 15, 1936. Following delivery the patient improved rapidly and was discharged June 3, 1936. In September, 1936, her blood showed 3,000,000 red blood cells per c.mm. and gastric analysis revealed:

	FASTING	15 MIN.	30 MIN.	45 MIN.	60 MIN.	75 MIN.	90 MIN.	105 MIN.
Free HCl	0	10	14	22	38	42	41	empty
Total HCl	5	16	25	39	61	63	61	empty

Baby Joan K.: was born May 15, 1936, weighing four pounds, fifteen and one-half ounces and was apparently in good condition. The infant received breast milk and a complementary formula. The infant's progress was good except for increasing waxy pallor. The liver was 4 cm. below the costal margin and the spleen 1 cm. below the costal margin. The blood count, on June 1, revealed a severe anemia. Therapy consisted of liver extract, antirachitics, orange juice, and ferrous iron therapy. The infant regurgitated moderately, especially orange juice and iron. Following transfusions her complexion would improve and listlessness would disappear, although mild temperature reactions occurred. Hemograms demonstrate the blood pictures of the mother and infant and their response to treatment.

#### DISCUSSION

Macrocytic anemia encountered during pregnancy has been divided into three types,<sup>6</sup> tropical nutritional anemia, true Addisonian anemia complicated by pregnancy, and macrocytic anemia induced by pregnancy. It is the latter type of anemia which concerns us here. It is a rare complication of the gravid state. Only one case has been encountered on the Maternity service of the Philadelphia General Hospital. Hematologically, macrocytic anemia of pregnancy is indistinguishable at times from "true" pernicious anemia. It is now generally believed, that this condition is due to a dietary deficiency and the old theory that this condition is due to some product of gestation is no longer tenable. Elsom and Sample<sup>7</sup> have produced macrocytic anemia by means of diets deficient in vitamin B complex, and prompt relief has been obtained by the administration of vitamin B complex and liver, with subsequent delivery of normal full-term infants. The response of our patient to liver therapy may be considered inadequate and her severe reactions to transfusions precluded their further use. The reticulocyte response was poor both during pregnancy and after parturition. The reticulocyte response as an index of effectual therapy is well recognized. Minot and Castle<sup>8</sup> state, "In the analysis of the physiologic basis of various types of nutritional deficiency anemias, daily observation of the course taken by the reticulocytes probably constitutes the best single criterion. Thus, in definitely anemic patients the failure of a reticulocyte response to appear after parenteral injection of liver extract or after oral administration of iron or orange juice may be taken to indicate that there is not a deficiency of these substances." We can, therefore, assume either that a specific need for the liver was not indicated or that an inadequate dose or an impotent

TABLE II. BABY JOAN K.

DATE, 1936	HEMOGLOBIN %	MILS R.B.C. C.M.M.	W.B.C. C.M.M.	MYELOCYTES	LYMPHOCYTES	SEGMENTERS	TOTAL NEUTROPHILES	LYMPHOBLASTS	LARGE LYMPHOCYTES	INTERMEDIATE LYMPHOCYTES	SMALL LYMPHOCYTES	TOTAL LYMPHOCYTES	MONOCYTES	EOSINOPHILES	BASOPHILES	LIVER EXTRACT C.C.	TRANSFUSION, BLOOD	ERYTHROBLASTS	POLYCHROMATOPHILIA	MACROCYTES	RETICULOCYTES	PLATELETS, THOUSANDS
5/30	25	1.41	14,600	0	0	34	60	0	2	0	24	26	11	2	1	0.0		+	+	+	1.0	320
6/1	20	0.96	12,200	4	0	40	72	0	4	0	16	20	6	0	0	0.0	65	+	+	+	1.0	300
6/3	25	1.25	16,300	12	0	36	82	0	8	0	10	18	0	0	0	2.0	120	+	+	+	1.0	340
6/4	25	1.10	14,200	8	0	32	86	0	6	0	8	16	4	0	0	2.0		+	+	+	1.0	300
6/5	78	3.98	11,200	0	0	44	72	0	6	0	14	20	4	4	0	2.0		+	+	+	1.0	340
6/10	50	2.20	9,800	0	0	34	66	0	4	0	6	12	18	4	0	2.0	60	+	+	+	2.0	302
6/13	35	1.82	10,200	0	0	38	63	0	2	0	8	32	22	3	0	2.0		+	+	+	3.0	100
6/16	25	1.36	15,200	8	0	22	40	0	10	0	22	32	28	0	0	2.0	60	+	+	+	2.5	60
6/18	30	1.60	12,900	0	0	16	37	0	45	5	2	58	3	0	0	2.0		+	+	+	5.0	80
6/21	25	1.26	10,000	0	0	7	6	5	83	1	0	80	1	0	1	0.5		+	+	+	3.0	100
6/26	35	1.80	10,100	0	0	10	14	4	70	2	4	80	4	2	0	0.5	60	+	+	+	2.5	120
6/29	40	2.10	10,000	0	0	8	18	0	26	0	42	68	12	0	0	0.5	60	+	+	+	1.5	150
7/11	45	2.41	9,800	0	0	20	30	4	10	6	40	60	6	4	0	0.5		+	+	+	1.0	160
7/13	52	2.52	8,000	0	0	26	38	4	6	0	44	52	6	0	4	0.5		+	+	+	2.5	220
7/15	50	2.48	9,200	0	0	30	44	4	10	6	30	50	4	0	0	0.5	50	+	+	+	1.0	180
7/16	52	2.58	7,300	0	0	40	56	0	10	4	20	34	10	0	0	0.5	20	+	+	+	2.5	220
7/18	50	2.60	8,400	0	0	16	34	6	10	10	30	56	6	4	0	0.5		+	+	+	2.0	224
7/22	70	3.16	9,900	0	0	18	22	0	18	0	46	66	8	4	0	0.5	40	+	+	+	1.0	230
7/23	70	3.20	8,900	0	0	20	30	0	14	16	30	62	6	3	0	0.5		+	+	+	1.0	230
7/30	75	3.35	8,800	0	0	23	42	0	4	10	36	50	5	3	0	0.5		+	+	+	1.0	240
9/23	78	3.77	8,000	0	0	20	42	0	4	6	16	26	12	0	0	0.0		+	+	+	1.0	250

## THE TREATMENT OF EARLY ABORTION\*

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THE term abortion is used to represent the loss of a pregnancy before twenty-eight weeks of gestation have passed. The term, however, is confusing because our present archaic laws require us to register as births all pregnancies terminating after twenty weeks of gestation. We are, therefore, using the term early abortion as meaning the expulsion of the products of conception before thirteen weeks, and we will confine our discussion to such cases. If the term late abortion is used, we mean the loss of a pregnancy between thirteen and twenty-eight weeks.

It has been stated by Taussig<sup>1</sup> that abortion is the greatest single factor in fetal and maternal mortality and also that one out of every four or five pregnancies terminates in fetal death through abortion and that two out of every five maternal deaths can be ascribed to an abortion. Macomber reports one abortion to every 3.4 confinements. Kapp 1 to 2.5 and Plass polling 81 country physicians says about 1 out of every 5 for the rural sections.

We have no way of obtaining the correct figure for this series but while these 1,114 early abortions were being handled, resulting in 985 completed cases, there were 258 late abortions and 12,294 deliveries in the Evanston Hospital. This gives a ratio of about 1 abortion to 9.8 deliveries. In the private practice of one of us (C. E. G.), early (4.9 per cent) and late (3 per cent) abortions combined were 7.9 per cent of all cases coming for care during the past nine years, in other words, 1 abortion to 11.6 deliveries.

The higher figures mentioned above may be representative of the country as a whole but cannot be taken as an example of what is true of all groups of people, as we shall show from a study of early abortions at the Evanston Hospital during the past fifteen years.

Among a fairly intelligent group of women who desire babies and who exercise good care in order to get them, the figures are much lower. The principal factor in abortion deaths is criminal interference and next comes improper conduct of abortion by the physician. If we eliminate the crime factor and if we accept the statement that fully 60 per cent of all early abortions are due to faulty development of the germ plasma, abortion at once becomes a minor problem.

A large factor in the incidence of abortion today is the lack of knowledge of such matters on the part of the laity. Our women know very little concerning the physiology of pregnancy. They attend schools with as high a scholastic ranking as those attended by the men, but the subjects taught and emphasized are not those pertaining to reproduction and

\*Presented at a meeting of the Chicago Gynecological Society, January 20, 1939.

extract was used. Nevertheless, the mother did improve after delivery, when there was a cessation of vomiting and diarrhea and better utilization of a balanced diet.

The deficiency factor which produced the anemia in the mother may possibly have been likewise deficient in the infant. It appeared that the maturation of the erythron was arrested at a fetal level, because of the infant's inability to utilize a factor which it could not obtain in utero. In fact, there appears to have been little response to combined therapy and the transfusions seemed only to carry the infant over until such a time as its own erythropoietic system could function at a more mature level. The infant's reticulocyte response was definitely poor in spite of marked anemia. Once a higher level of maturation of the infant's red blood cells was attained, probably conditioned by dietary intake of the deficient factor, steady improvement was noted. Oddly enough there was not an "adequate" reticulocyte response in the recovery phase. We can only say that the erythropoietic system was either depressed or inhibited in some inexplainable manner and improvement occurred only when this was overcome. Why such factors should work selectively on the erythropoietic system does not seem explainable, except by some mechanism such as produces pernicious anemia in adults. The anemia of the infant may be difficult to classify. We believe that we may be justified in calling this a "hypoplastic" anemia, but feel as many others have before us, that it is more important to arrive at an understanding of the process than to give it a name.

#### SUMMARY

The relationship of macrocytic anemia of pregnancy with a severe anemia of the newborn is herein reported, with a discussion of the etiologic factors involved. We believe that the anemia of both the mother and the infant is due to a dietary deficiency.

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are not in a position to evaluate this product. After reading the literature on its use in the prevention of abortion, we concluded that there has been no satisfactory clinical work done with it when it is used alone in treating a series of such cases.

We still believe that the greatest single factor in prevention is bed rest with sedation. This report covers a period of fifteen years and during the greater part of this period neither hormone treatment nor wheat germ oil had been in use. From Table I, it is found that 135 patients entered the hospital with a diagnosis of threatened abortion and 124 of these left the hospital still pregnant. The 11 who aborted did so in the first five-year period.

One often hears figures on the incidence of abortion quoted and in Table VI, the record is shown of private patients treated by one of us during the past nine years. Our patients come early for care—about eight or nine weeks pregnant at their first visit. If only approximately 5 per cent have early abortions and three-fifths of these are to be regarded as developmental defects, then this group of women had a loss amounting to 2 per cent that might have been saved during early pregnancy.

It is essential in the proper care of such cases to make a fairly accurate estimate of the amount of blood lost. Fatalities have occurred because no one was aware of the importance of this knowledge, and often the physician has been compelled to interfere when a false statement was being made by the patient or her attendants. Regardless of how slight the bleeding, the patient should be instructed to use a vessel and to save all pads so that the physician can see them and make his own deductions with reference to the amount of blood loss.

Now we come to the question of how much blood loss should be tolerated before terminating the pregnancy. The size of the uterus, the age of the patient, the parity, the general state of health and the patient's reaction, all must be taken into consideration. Personally, we feel that all things considered, early interference will give the best results. This seems to be the opinion of most observers whose work is being reported in this paper. The 1,114 patients upon which this paper is based were treated by 49 doctors, although 73 per cent of these patients were attended by 6 men. The maternal mortality for the entire group, including 65 classed as criminal, is only 0.35 per cent, and if we deduct the 129 patients who left the hospital still pregnant, the mortality is 0.40 per cent. The maternal mortality for 751 operative cases, exclusive of criminal abortion, is only 0.26 per cent. This compares favorably with our maternal mortality for delivery which was 0.17 per cent for the past ten-year period.

Before considering evacuation of the uterus, one must always attempt to ascertain the presence of infection, for the majority of all fatalities are due to sepsis. Hillis and others have made the rule that the temperature should be normal for five days before curettage, if this may be possible. It is only the rare case that is infected and at the same time bleed-

the home. The men, on the other hand, come to positions in life well equipped with a vast store of information and much better prepared to face the problems they meet. If we could teach our women the care which is sometimes necessary to retain an early pregnancy, rather than be called upon at the last minute to find the patient aborting and referring to the accompanying flow as "menstruation," we would probably have fewer abortions. The average young woman has a fair knowledge of contraception, but she knows little or nothing of the ravages of abortion and gonorrhea and only because she has received no such teaching.

This paper deals with the management of early abortion and not its cause, hence no further comment will be made on prevention. Suffice it to say that we probably have only 40 per cent of the cases of threatened abortion that could or should be prevented—the embryos in the other 60 per cent have not developed properly and should be expelled.<sup>2</sup>

A factor in prevention still holding number one position is bed rest and whenever one is called to attend a patient having symptoms of abortion, he should insist upon bed rest and the patient should be kept in bed until several days have elapsed with no further signs of bleeding or cramps.

Since Lackner<sup>3</sup> and others have shown that morphine and its derivatives may cause uterine contractions, the authors have used pentobarbital as a sedative, with good results. Morphine and codeine many times may also cause nausea and vomiting; the barbiturates do not.

A great deal has been written about the use of progesterone or the luteinizing hormone and its ability to quiet uterine contractions, thus preventing abortion. From a clinical standpoint it seems to do some good; however, it is very difficult to prove its effectiveness clinically, and it is also quite expensive. In our experience, there have been times when we felt certain that it had a quieting effect upon uterine contractions even in women with a history of repeated abortions and whose personal reactions and experiences were worth considering. On the other hand, one of us has seen two cases where its administration led to a prompt increase in pain and bleeding, followed by rapid abortion. Our knowledge of the endoerines and our ability to prepare them are still in the embryonic stage of development.

Because these products are so expensive, we have during the past year been giving them hypodermically at the beginning of the treatment only—the treatment is then changed to corpus luteum by mouth. However, when a patient first bleeds, and more especially if she has cramps, she is given three and four units of proluton every twenty-four hours regardless of the cost. This is accompanied by fairly large doses of pentobarbital, 3 to 4.5 gr. at night and 1.5 gr. about noon. As time goes on, the amount of proluton is decreased and after several days the patient is given 5 gr. of lutein by mouth three times a day and the sedative is stopped. We prefer that the patient go to the hospital if at all possible; if not, she is asked to have a nurse with her at home. If neither is possible, the injections are given by a visiting nurse or the attending doctor.

We have had little experience with wheat germ oil. It has been used, but always in conjunction with proluton, calcium, and sedatives, and we



TABLE III. DURATION OF SYMPTOMS BEFORE ENTERING THE HOSPITAL

DIAGNOSIS	NUMBER	DURATION OF SYMPTOMS AVERAGE NO. OF DAYS	
		2 WEEKS AND OVER	UNDER 2 WEEKS
Incomplete	643	160 av. 24.2 days	413 av. 3.3 days
Threatened	135	92 av. 25.4 days	65 av. 2.4 days
Inevitable	73	12 av. 23.1 days	50 av. 3.1 days
Complete	108	14 av. 36.2 days	72 av. 3.0 days
Therapeutic	74	6 av. 58.0 days	1 av. 7.0 days
		(1928-1938)	
Criminal	65	17 av. 26.8 days	32 av. 4.6 days
Missed	16	3 av. 28.0 days	5 av. 3.6 days
		(1928-1938)	
Total	1,114		

The reasons presented for therapeutic abortion are given in Table IV, and we presume some criticism will be forthcoming as thyroid disease, heart disease and diabetes are all questionable indications. It is difficult, even for one examining the charts, to tell fully the extent of the disease; however, the rule that at least two men must state in writing that the procedure is absolutely necessary, has always been followed.

The most difficult cases to manage and those showing the highest mortality are the cases of criminal abortion, either complete or incomplete. Only about 6 per cent of our cases were classified as such but these fur-

TABLE IV. REASONS FOR THERAPEUTIC ABORTIONS

There were 74 therapeutic abortions during this fifteen-year period. Sixty-four were curetted and ten had hysterotomy done.

Causes for therapeutics were as follows:

Toxemia	11	Tuberculosis	8
Thyroid	6	Pernicious vomiting	9
Psychoneurosis	2	Pernicious anemia	1
Heart	18	Carcinoma of bowel	1
Kidney	12	Osteomyelitis	1
Diabetes	1		
Strangulated ovarian cyst and recent laparotomy-----			1
History of malformations-----			3

TABLE V. CRIMINAL ABORTIONS\*

	FIRST 5 YR.	SECOND 5 YR.	THIRD 5 YR.
Operated	7	12	2
Spontaneous	9	2	3
Not reported	5	17	8
Total 65	21	31	13

\*Note: Deaths (2), both unoperated.

TABLE VI. INCIDENCE OF ABORTION—PRIVATE PATIENTS

During the nine-year period just ended, 4.91 per cent aborted before 13 weeks, of these:

37 per cent were complete spontaneous

63 per cent were incomplete and required dilatation and curettage

Three per cent terminated between thirteenth and twenty-eighth weeks, of these:

69.7 per cent were spontaneous

30.3 per cent were incomplete and required operative interference

ing enough to endanger the patient's life. However, there are many patients who should not be operated upon even after five days of normal temperature when laboratory evidence may indicate there is no infection.

Most women desiring children and willing to cooperate in their treatment are not infected, as is shown in Tables I and II; however, we did show reasonable conservatism by waiting, in 204 patients, an average of from three to four weeks before they were admitted to the hospital. These figures are shown in Table III. The ability to detect a hidden infection or a potentially infected case requires not only thorough laboratory work but considerable clinical experience as well.

The routine followed at the Evanston Hospital is as follows:

If possible we wait until the cervix is somewhat dilated. Morphine  $\frac{1}{6}$  gr. and atropine  $\frac{1}{500}$ th gr. is given by hypodermic before the patient goes to the operating room; then she is given a general anesthetic using ethylene. We find that the average patient does not like to be conscious throughout any operative procedure if sleep is possible and safe, and so we have available at the Hospital four trained anesthetists. The patient is then draped, and after this the contents of the uterus are removed with placental forceps. The uterus is then injected with pituitrin by means of a long needle passed through the cervix. A large sharp curette is then used to remove any fragments of placental tissue and the uterus and vagina are packed with gauze. If we have interfered because of bleeding and we suspect contamination, the curettage and packing are dispensed with.

TABLE I. OPERATIVE INCIDENCE OF EARLY ABORTION

ENTRANCE DIAGNOSIS	NUMBER	OPERATED	NOT OPERATED	
			SPONTANEOUS	REST PALLIATIVE
Incomplete	643	605 C (93.7%) 2 hysterectomies 1 laparotomy	26 (4.0%)	9
Threatened	135	4 C (3.0%)	7 (5.2%)	124 still pregnant
Inevitable	73	51 C (70.0%)	19 (26.0%)	3 still pregnant
Complete	108	—	108 (100.0%)	—
Therapeutic	74	64 C (85.5%) 10 hysterectomies	—	—
Criminal	65	21 C (32.0+%)	14 (21.0%)	—
Missed	16	14 C (87.5%)	—	2
Total	1,114	759 C (69.0%)	174 (15.6%)	14

TABLE II. MORBIDITY AND MORTALITY OF EARLY ABORTION

ENTRANCE DIAGNOSIS	NUMBER	DEATHS	FEBRILE CASES 101 UP 1 DAY OR MORE	AV. NUMBER DAYS FEBRILE
Incomplete	643	1	72 (11.0+%)	1.6
Threatened	135	—	6 (4.4%)	2.6
Inevitable	73	—	5 (6.8%)	1928-1938
Complete	108	—	11 (10.0+%)	1
Therapeutic	74	1	15 (2.2%)	4.8
Criminal	65	2	22 (33.8%)	1.4
Missed	16	—	1 (6.2%)	5.2
Total	1,114	4 (0.35%) *(0.40%)	132 (11.2%)	—

\*Deducting 129 who went home pregnant.

2. If one accepts the fact that fully 60 per cent of all early abortions are due to faulty germ plasm, we must conclude that only 2 per cent of our women will lose their pregnancy during the first three months, which might otherwise have been preventable.

3. The risk of early abortion should be below one-half of 1 per cent.

4. A high operative incidence in such cases does not appear to increase morbidity or mortality.

5. The mortality for early abortion, exclusive of criminal abortion, should be no higher than that for delivery.

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#### DISCUSSION

DR. DAVID S. HILLIS.—I desire to report on part of the year's work at Cook County Hospital on abortions, approximately a six months' experience. Patients at this hospital are very different from those considered in Dr. Galloway's report. Accurate information regarding the relative number of spontaneous and criminal abortions is practically impossible to obtain, but we do know that a large proportion of the cases in Cook County Hospital are criminal abortions. The policy in this hospital is to treat all cases on this basis; any mistakes made are on the side of safety. It is well known that the second invasion of the aborting uterus is dangerous until the patient has been temperature-free for five days and during this year we have found one exception to this rule. Approximately four out of five of all patients admitted are fever-free and are classed as nonseptic cases. About 75 per cent of these are allowed to empty the uterus themselves with the aid of quinine and pituitrin in small doses. If the bleeding is prolonged or excessive and involution does not progress normally, the uterus is evacuated with a dull curette or ovum forceps after the temperature has been normal for five days. Septic abortions are not emptied except when hemorrhage endangers life. When bleeding is severe the os is practically always found to be well dilated, permitting removal of the contents by means of ovum forceps and with a minimum of trauma. If severe bleeding does not occur, supportive treatment, intravenous fluids, blood transfusions, and sedatives are used. Sulfanilamide is now being given to alternate cases in the ward.

Routine packing of the uterus is not done on this service. The uterus is packed only in rare cases in which bleeding is so profuse during a curettement that it must be stopped immediately. Packing the uterus interferes with contraction, retraction, and drainage, and if the uterus is empty it will not bleed. During the past twenty-five years in this ward no uterus has been packed except for hemorrhage.

The deaths on this service belong to two groups:

1. Those who are admitted in a terminal state with peritonitis or septicemia. The deaths in 1938 included seven such patients who died within twenty-four hours.

2. The second group that contributes to mortality are those that are curetted in the ward on account of excessive hemorrhage. One patient died following curettage after the temperature had been normal for five days. A gangrenous placental polyp was found at post mortem. This case in our experience is one of the rare exceptions to the rule that it is safe to curette a patient after five days of normal temperature.

DR. WILLIAM H. BROWNE.—At the Research Hospital we have an entirely different problem from that in private practice, in a private hospital or in a large charity hospital such as the Cook County. Because of the dearth of beds for obstetrics those patients who might come in as emergencies are not admitted but are usually shifted to the Cook County Hospital unless they have been previously regis-

nished 50 per cent of the mortality. It is a fairly safe procedure to always refrain from any surgical interference in such cases unless driven to it by hemorrhage or some other emergency. However, as can be seen in Table V, at least 21 of the 65 patients were operated upon. The two patients in this group who died were not operated upon.

Brief case reports of the four deaths in the series of 1,114 cases follow:

CASE 1.—Patient, aged 31, para iv, was about seven weeks pregnant. She entered the hospital in shock, March 5, 1929. Pulse 110. Temperature 98.6° F. At times her pulse was not obtainable. Symptoms: bleeding four days, Hg 57 per cent, red count 3,290,000, she was admitted at 10 A.M. Dilatation and curettage and the uterus was packed at 10:15 A.M.; 2,000 c.c. of dextrose in Ringer's solution 5 per cent during afternoon. At 5 P.M. her temperature was 104° F.; pulse, 132; respiration, 26. She died at 9:45 P.M. Microscopic diagnosis: Infected and necrotic placental tissue. Caffeine by hypodermic 6 times. No morphine. Not transfused. No autopsy.

CASE 2.—Patient was admitted Jan. 19, 1930 and died January 20. Patient said a midwife inserted a rubber catheter two days before she entered the hospital and the following day the midwife did a curettage and packing. Generalized peritonitis when first seen. Temperature 104° to 106° F. White blood count 21,000. Pulse 120 to 156. Autopsy: Ectopic pregnancy. Fibrinopurulent hemorrhagic general peritonitis and metritis. Blood culture: Hemolytic streptococci. (The midwife was convicted and sentenced.)

CASE 3.—Patient entered the hospital on the evening of Aug. 20, 1930 and died on the morning of August 22. She was three months pregnant. She had been vomiting for six weeks. She was at home and not attended by any physician. Urine 40 per cent albumin, casts, red cells and sugar +. Temperature 98.6° F. Pulse 90 on entrance. 3000 c.c. of dextrose in Ringer's by vein and 1000 c.c. normal salt solution by proctoclysis first twenty-four hours. She passed only 25 c.c. of urine. Pulse went up to 120 and patient passed into shock. Diagnosed acute nephrosis. Uterus was emptied as quickly as possible. Patient remained in shock and died five hours later. Considerable blood was lost but a transfusion was not given.

CASE 4.—Patient, aged 27, para i, two months pregnant, entered the hospital July 26, 1935 and died August 6. She inserted a slippery elm herself and fever began twenty-four hours later. She was admitted to the hospital three days later, and developed general peritonitis. Usual peritonitis treatment was given with no surgical procedures, except numerous venoclyses and two blood transfusions. No autopsy was performed but the coroner stated that the uterus contained multiple abscesses and infected necrotic placental tissue.

#### COMMENT

During the past fifteen years, 1,114 cases of early abortion were cared for at the Evanston Hospital. Four patients died, a mortality rate of 0.35 per cent for the entire series or 0.40 per cent if 1,129 patients who were discharged still pregnant are eliminated. Sixty-nine per cent of the entire series were operated upon. Deducting the therapeutic abortions and those still pregnant when discharged this percentage changes to 86.3. The total morbidity was 11.3 per cent. During the same period there were 6 hydatidiform moles and 95 ectopic pregnancies and 258 late abortions.

#### CONCLUSIONS

1. Among a fairly intelligent class of women where a large majority want babies, early abortion occurs in about 5 per cent and late abortion in about 3 per cent.

progestin is used more in cases of habitual abortion. Bed rest, I feel, is the most important part of the treatment. Wheat germ oil and thyroid extract are also incorporated into the treatment of habitual abortion.

In a series of 397 cases the upper incidence of intentional abortion was 14 per cent; in another 6 per cent the abortion was attributed to toxemias, habitual abortion, or over-activity. There were 83 therapeutic abortions or 20 per cent included in this group of 397 cases.

Our treatment of inevitable and incomplete abortion consists of bed rest, which is the most important part of the treatment. If the symptoms are mild the patient is usually treated at home rather than being brought to the hospital, because we feel that possibly the trip to the hospital may be a strong factor in changing a threatened abortion into an inevitable abortion. On admission the patient is kept at bed rest for seventy-two hours, watching the temperature, pulse, and the white blood count. Abdominal examination is done to rule out any extension of infection to the parametria and peritoneum. The uterus is evacuated at the end of this period if the above criteria are normal. If abnormal, observation is continued until the patient is normal. If the bleeding is profuse the uterus must be emptied at once. General supportive treatment is given. An important aid is the use of blood transfusions, preoperatively as well as post-operatively. On admission to the hospital 21 per cent of the 397 patients had fever.

At operation careful examination is made to rule out any extension of infection, pelvic abscess, or adnexal pathology. The cervix is exposed and a uterine culture is taken. It is interesting that 40 per cent of positive uterine cultures were due to anaerobic streptococci and only 6 per cent to hemolytic streptococci. The evacuation of the uterus is done with a sponge or ovum forceps and a large dull curette. We usually give 1 c.c. of pituitrin into the uterus before curetting. The uterine cavity is swabbed out with an iodine soaked gauze sponge. We avoid any packing of the uterus and any extensive instrumentation. The uterus was emptied in 75 per cent of our series. If we exclude the therapeutic abortions the incidence of emptying the uterus is 69 per cent.

Postoperatively, general supportive treatment is given and again I emphasize blood transfusions. We routinely transfuse a patient if the hemoglobin is below 10 gm. Of course, if the patient shows evidence of infection postoperatively, she is treated as a case of peritonitis. Otherwise, general supportive treatment is the routine.

The average number of postoperative days is four for nonseptic cases. Sulfanilamide is used in our clinic only in cases of proved etiology and where the organism is known to respond to sulfanilamide.

The morbidity was 13 per cent. Three patients died, two having been admitted with obvious severe infections, self-induced. In these two cases no operative treatment was carried out by us. The third patient who died had a therapeutic abortion. However, the death was due to hyperemesis gravidarum, the patient being comatose at the time of operation and dying eight hours later.

DR. HAROLD O. JONES.—I wish to present the other side of this problem. First, it seems to me that the results of the methods of treatment are questionable. We are convinced that if a certain number of these patients are left alone a great many pregnancies will be saved. Time will show whether it is a threatened abortion or an inevitable abortion. Consequently I think they are entitled to all the time they need to keep the products of gestation in the uterus.

Second, we believe that infection is associated with practically all these conditions. There is no way of determining the virulence and the degree of infection. Our plan of management is just the opposite from what was stated here tonight. Our patients are treated conservatively and left absolutely alone. If they come in bleeding profusely and there is tissue in the cervix, the tissue is removed but on no account do we curette.

The other thing that I think is important is this: from the paper of the essayists one would think this a very simple procedure. If one knew the number of cases of perforation of the uterus that occur following curettement, one would be very cau-

tered in the dispensary. Consequently, the incidence of abortions at the Research Hospital is astoundingly low. Furthermore, these patients apparently wish to keep their pregnancies because they have come to the dispensary and registered and subsequently developed hemorrhages. We do not have many criminal abortions. In the last six years 54 patients were admitted to the hospital for the management of abortions. This does not constitute as early a group as Dr. Galloway reported and is an incidence of slightly less than 1 per cent. This low figure is explained by the fact the patients register first.

We feel in the management of these cases where the onset is presumably spontaneous that the point of departure is the life or death of the fetus. Consequently, if we can determine that the fetus is alive and if no abortion is in progress as evidenced by rectal examination, all our efforts are conservative in the attempt to save the pregnancy. If, after twenty-four hours, we find that the fetus is probably dead and retained, all efforts are aimed at aiding the uterus in evacuating its contents. This diagnosis of the life and death of the pregnancy is arrived at from the history, symptomatology, and by the use of the Friedman test for pregnancy. If the test comes back positive we know that we have presumably living, growing placental tissue. We are not sure that the fetus is still alive, but we feel that in a fair percentage of cases it is. If we get a negative reaction we feel that the diagnosis of suspected abortion is questionable. Those cases are treated actively to check the bleeding. There is an intermediate group that gives a faint reaction on the ovaries of the rabbit. Dr. Rezek has reported this reaction as a dead fetus reaction. If the ovary of the rabbit is placed on a slide and held up to the light you will see a faint circle of hyperemia around the follicle. That test is not infallible but at the Research Hospital it has enabled us to make a diagnosis of a dead fetus and to switch the management from conservative to radical, and enable the patient to make a prompt recovery.

A certain group of cases have been treated with progestin. The morphine that Dr. Galloway mentions is used sparingly on the basis that it may produce uterine contractions. We feel that the diagnosis of a dead fetus is essential in the management of abortion, so that we will not be giving progestin to hold a dead fetus in the uterus.

DR. FRED O. PRIEST.—We have reviewed the charts of early abortions at the Presbyterian Hospital during the past five years. These include the private patients, the hospital clinic obstetric patients and those from the Out-patient Department of Rush Medical College requiring hospitalization. Our number of incomplete abortions completed by medical management is small, since these patients, private or otherwise, are not hospitalized if bleeding is controlled by oxytocics given at home. The small number of threatened abortions is due to the fact that, first, all uncontrolled cases are transferred to the inevitable or incomplete classification and are listed in the above column; second, most of our threatened abortions are treated at home, even among private patients. This management consists of absolute bed rest, sedation, both morphine and barbiturates and more recently wheat germ oil. In private practice proluton is also given. Patients who have had repeated abortions are placed on a modification of this regime when pregnancy is diagnosed, even before symptoms of a disturbed pregnancy exist. We believe that conservative treatment should not be continued where symptoms are prolonged or where bleeding becomes heavier than at an ordinary menstrual period. We are, of course, influenced in this by the length of the sterility period and the patient's desire for the child.

DR. PAUL W. WOODRUFF.—At the Chicago Lying-in Hospital the same remarks can be made about the type of patients as Dr. Browne made. Our cases are mostly registered cases, thus our incidence of criminal abortion and the general incidence of abortion are low. I will limit the discussion to the treatment of incomplete and inevitable abortion.

The treatment of threatened abortion is similar to that given by Dr. Galloway except that we use morphine and atropine as sedative and antispasmodic drugs, while

# STUDIES ON RECONSTRUCTION OF THE FALLOPIAN TUBE\*

## PRELIMINARY REPORT OF AN ORIGINAL TECHNIQUE

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OF THE many causes of sterility in the human female, tubal obstruction is the outstanding one that lends itself to surgical intervention. The number of methods devised and employed are far too numerous and diverse to be considered at this time. Since Martin<sup>1</sup> and Schroeder attempted the first recorded plastic operations in 1885, interest in this type of surgery has been more or less sporadic until recently. During these past few years, the various techniques have been modified and perfected to the point where the sum total of end results is fairly good, but certainly not satisfactory. For example, Greenhill,<sup>2</sup> as a result of a recent questionnaire sent to most of the outstanding gynecologists of this country, states that plastic operations for the relief of tubal obstruction result in 4.4 per cent pregnancies and 2.2 per cent live term babies. While the percentage of patent tubes resulting from such operations is undoubtedly much greater, and while results in individual clinics that specialize in this type of surgery are much better, the sum total of the results still leaves much to be desired.

The methods most commonly employed today for the surgical relief of tubal obstruction may be summarized as follows:

1. The so-called "circumcision" operation, in which the closed fimbriated extremity of a tube is amputated, the mucosa being euffed back over the distal portion of the serosa.

2. The implantation operation. In this procedure the tube is divided distal to the point of obstruction and the proximal portion of the tube which contains the point of obstruction is sacrificed by excision. The proximal end of the patent portion of the tube is then passed through an opening in the uterine cornua made either by coning out or by incision, so that it again establishes a passage connecting the uterine and peritoneal cavities.

3. The various modifications of Estes' transplantation of an ovary into a cornual incision which opens into the uterine cavity.

4. A little used procedure is that of excision of the point of obstruction, with subsequent end-to-end anastomosis of the cut ends of the tube.

There seem to be two outstanding reasons for the failures which follow the use of these procedures, assuming that other factors are favorable to conception. The first of these is postoperative closure of the tube, due either to the formation of adhesions within the lumen of the tube, or to adhesions between the fimbriated end and some

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tious about doing a curettage. Another thing that seems to be very important is what happens to these patients afterwards. That is not determined when they leave the hospital. What I contend is that there are a large number of patients in whom sterility follows curettement of the placental site. That condition does not exist if the uterus is allowed to empty itself of the products of conception.

DR. N. S. HEANEY.—A point I wish to stress is, that habitual abortions are not always due to difficulty with the ovum or the corpus luteum, that sometimes there is an injury to the cervix due to a past delivery, abortion, or operation. I like to examine patients while they are aborting, for then the cervix is dilated and it can be entered, palpated, and inspected, and its integrity or injury definitely established, while if the patient is examined weeks later through the undilated cervix, the diagnosis is often doubtful. In such cases also the loose, soft, dilated tissues can be drawn together easily and a better repair insured than if the patient is treated "conservatively" during the act of abortion and examination and repair made after her convalescence.

DR. MARK T. GOLDSTINE.—I think the pulse is much more of an indicator of what is going on than the temperature. The pulse is much more subject to change; even though the temperature is normal for five days and if the patient still has a rapid pulse I believe it is a contraindication to go ahead with the operation. Many of our patients with the worst septic abortions die with subnormal temperatures but with a very high pulse rate.

DR. GALLOWAY (closing).—I agree with Dr. Hillis that a second invasion of the uterus is very dangerous. It is a rule in all surgery that a second procedure is more dangerous than the first. If we can do everything at the first sitting, we must do it. Packing the uterus is much deplored, but we feel that if the uterus is packed in the clean case, it helps to clean it up and it helps to save the occasional bleeding that would occur if it were not packed. We cannot see, from our figures, that packing causes any harm. Dr. Hillis' figures seem to me to indicate that the ratio of abortions in the Cook County Hospital is very high, as I suppose it naturally would be.

Dr. Browne's figures are not comparable to the figures in private practice. I agree that rectal examination is the only type that should be made. We do the Friedman test quite often. We have not much confidence in the dead fetus reaction. It must be remembered that the Friedman test costs the patient six dollars, and there has to be a definite indication for it before she is required to spend that amount.

Dr. Priest's figures run quite like ours, 201 out of 270 threatened incomplete abortions were curetted.

Our paper is not complete, especially as to treatment. When Dr. Woodruff mentioned thyroid extract, he is quite right. We use all methods. We try everything to prevent abortion. I think our figures in private practice bear this out. If we only list one in twenty in early pregnancy, it compares very favorably with the figures of the country as a whole. I think we have erred in the past in not doing more transfusions.

As Dr. Jones remarked, I would also like to emphasize that although we seem to have a high operative incidence, we do all that we can to save the pregnancy. It is to our advantage to have a child instead of an abortion. We think if you allow a patient to go too long in an attempt to empty her own uterus, it will not be long before she is infected. We think that by emptying the uterus early there is much less chance of having infection. Perforation does occur but it is rare.

I think Dr. Heaney's remarks about cervical repair are well taken. I have seen patients abort that would not have aborted if they had been taken care of from a gynecologic standpoint before they became pregnant. If we see a patient in that condition, we should stress the fact to her that she is liable to abort unless she puts herself in condition before she becomes pregnant again.



## OPERATIVE PROCEDURE

An especially devised sheath of the Lindeman type (Fig. 1), the end of which had been ground to a round dull point was gently manipulated down the lumen of the tube for approximately 2 cm., after which the two inner trocars were removed. A long, fine, straight needle (Fig. 1), with 0000 chromic catgut attached was then passed through this sheath and out through the tubal wall, close to the mesosalpinx. With this piece of catgut in place, and protruding from the end of the tube, the sheath was removed. A sheet of allantoic membrane 4 by 6 inches was then gathered in the center in the same way one would pick up the center of a handkerchief. About this central point was tied the end of the suture which protruded from the fimbriated end of the tube. The fimbriated end of the tube was then gently held with gauze covered fingertips, while gentle traction was exerted upon the needle end of the suture, resulting in the passage into the lumen of the tube of a considerable

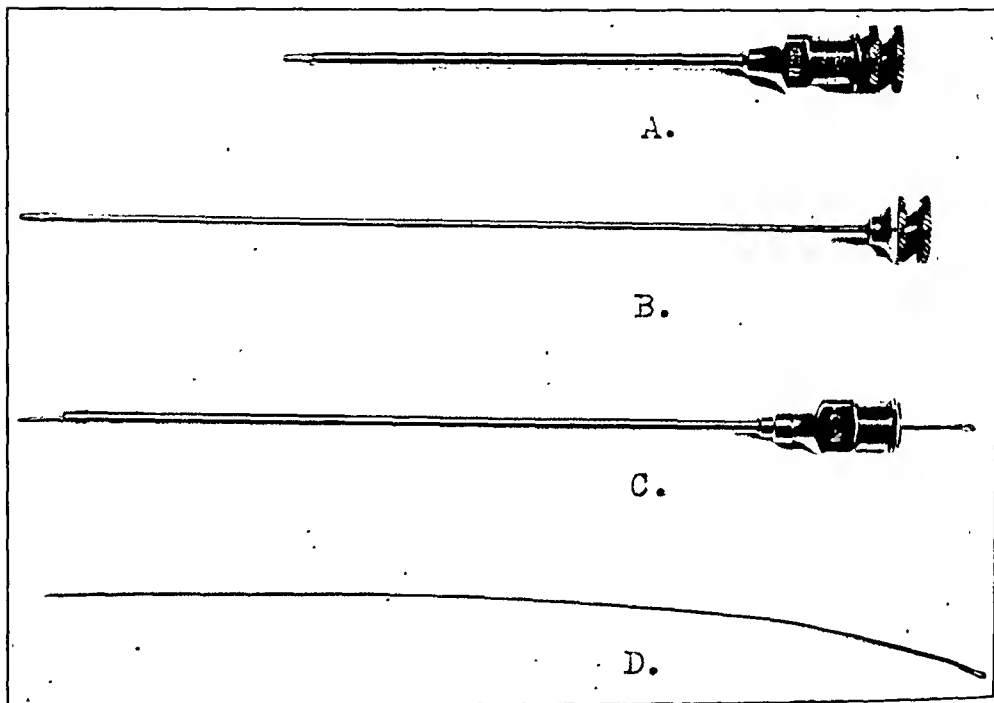


Fig. 1.—(A) Assembled short sheath and trocar for use in fimbriated end obstructions. (B) Long trocar to fit in (C). (C) Long sheath with needle inserted. (D) Flexible type of needle employed.

portion of the allantoic membrane. The remaining portion of the membrane protruded in a loose, pliable mass from the fimbriated end. This portion was then spread outward and downward over the serosa of the tube in such a manner as one would close an umbrella upon the handle. This resulted in the membrane completely covering the raw orifice of the tube, and at the same time protecting the distal portion of the tube against the formation of adhesions to surrounding structures. The various corners of the free edge of this membrane were then attached to the serosa of the tube and to the surface of the mesosalpinx with fine catgut, in order to hold it in place. The suture which had been placed through the tubal wall was likewise attached to prevent extrusion of the membrane due to tubal peristalsis. This procedure is outlined by steps in Fig. 2.

The experimental operation which was carried out in an attempt to determine the results which might be obtained in cases of isthmal obstruction, was as follows:

A  $\frac{1}{2}$  cm. segment of the middle of the tube was excised in the same way one would excise a point of obstruction in the Fallopian tube of the human being. A special sheath (Fig. 1) was then passed into the fimbriated end of the tube, through

adjacent structure. The second reason is the failure of an ovum to reach the tubal ostium. This latter reason has gained considerable importance in view of the recent work of Westman,<sup>3</sup> who has clearly demonstrated that the normally functioning Fallopian tube applies itself to the ovarian surface at the time of ovulation in its quest of an expelled ovum.

With these facts in mind, it can be seen that any operative procedure which results in a material shortening of the Fallopian tube will definitely interfere with its function. Thus, if any portion of a tube is sacrificed, the fimbriated end will be withdrawn a corresponding distance away from the ovary, and the delivery of an ovum into the tubal ostium will become considerably less likely. As the length of the extirpated tubal sector is increased, the probability of an ovum finding its way into the tube is correspondingly decreased. If the point of obstruction in such a case is found to lie in the outer half of the tube, and such a tube is reconstructed by the implantation technique, nothing more than a fimbriated stump is left protruding into the peritoneal cavity.

The same basic principles apply to the "circumcision" operation, for here the length of the tube is decreased by the amount of the tube amputated, plus the length of the mucosal cuff which is turned back over the serosa.

In an effort to partially overcome this marked shortening of the tube as a result of operation, we performed a number of end-to-end anastomoses in *Macacus rhesus* monkeys, using bone wax, chromic catgut, and plain catgut in the tubal lumen to preserve its continuity. None of these substances was satisfactory, due to failure of absorption, inflammatory reaction, or focal constriction of the tube at the site of anastomosis. In addition to these objections, it was also found that extensive peritubal adhesions occurred in every case. It was thought that these resulted from digital and instrumental manipulation of the tubes during the operation.

At about this time, a substance became available which seemed to hold considerable promise, namely, prepared sheets of allantoic membrane, which are tough and easy to handle, yet offer a maximum amount of pliability. This material was found to cause a minimum amount of inflammatory reaction, as will be demonstrated later. Bearing these advantages in mind, two surgical procedures were devised which allowed of its use in the reconstruction of tubes which were obstructed either at the fimbriated extremity or along the course of the extranterine portion.

The fimbriated end type of obstruction was duplicated as nearly as possible by traumatizing and closing the ends of the tube several weeks before the repair was to be carried out. When subsequently repaired, one tube was circumcised and cuffed according to the technique described by Holden and Sovak,<sup>4</sup> and others, while the opposite tube was treated in the manner to be described below. The end-to-end type of anastomosis was carried out upon normal tubes, no effort being made to produce an antecedent obstruction.

the lumen of the distal segment of the tube, and into the lumen of the proximal segment of the tube for a distance of about 1 cm. The needle with catgut attached was then passed through the sheath in the same manner as previously described. The two portions of the tube were then anastomosed end-to-end by the use of 0000 chromic catgut sutures which were passed through the serosa, muscularis, and mucosa. This procedure is outlined in Fig. 3. The sheath was then withdrawn and the allantoic membrane pulled through the distal lumen and into the proximal lumen in the same way as described for the previous operation. If the protruding portion of membrane was not sufficiently long to cover the point of anastomosis, another piece was sewed in place over this area. Before the abdomen was closed, a small amount of amfetin, or concentrated bovine amniotic fluid, was introduced into the peritoneal cavity to help prevent formation of postoperative adhesions.

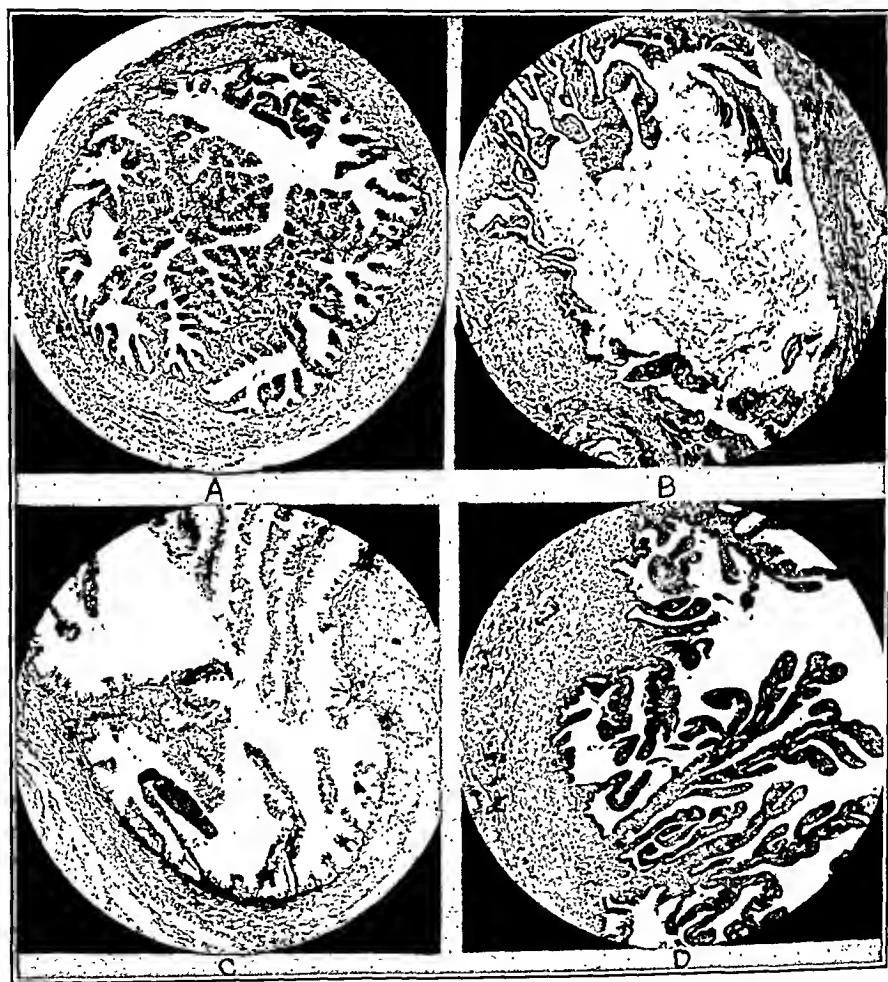


Fig. 4.—(A) Normal tube of *Macacus rhesus* monkey. (B) 6 weeks after introduction of bone wax into lumen. (C) 6 weeks after introduction of plain catgut. (D) 6 weeks after introduction of chromic catgut.

### RESULTS

The operated tubes were removed at varying intervals following operation and studied carefully to determine the relative amount of inflammatory reaction which followed the use of the various substances.

Fig. 4(A) is a cross section of a normal Fallopian tube of a *Macacus rhesus* monkey.

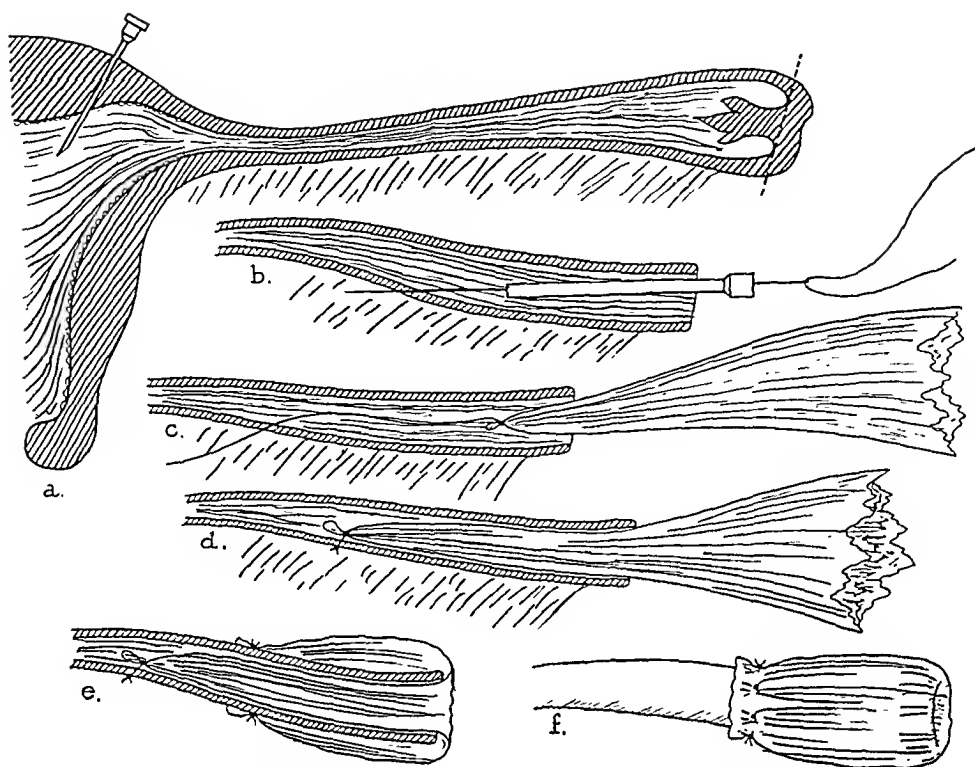


Fig. 2.—Steps of operative procedure employed for fimbriated extremity obstruction.

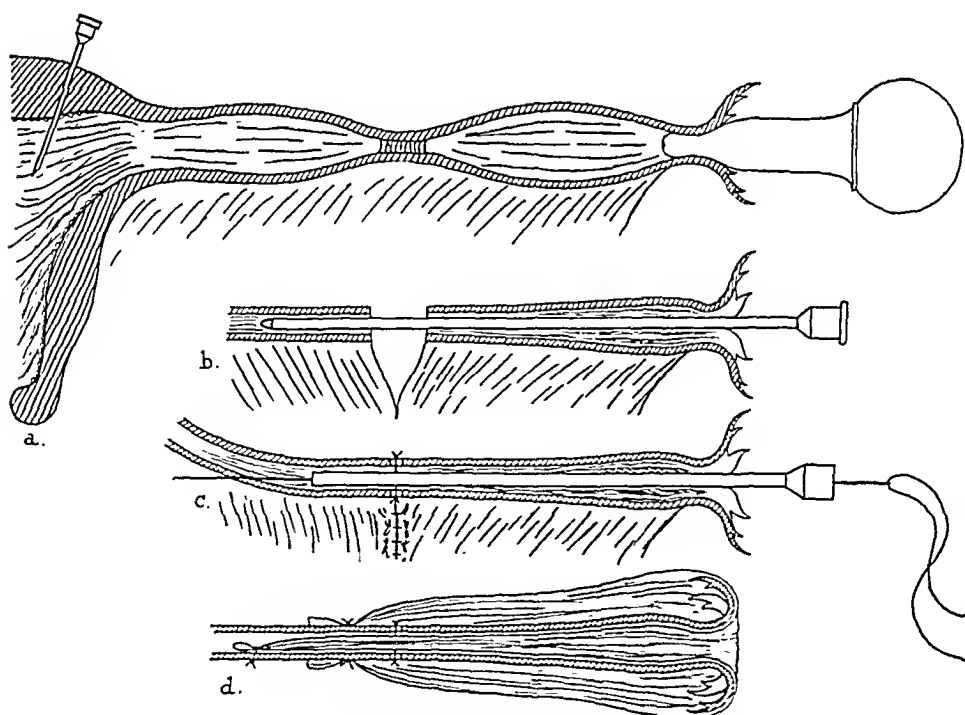


Fig. 3.—Steps of operative procedure employed for midpoint obstructions.

These sections demonstrate clearly that chronic catgut causes far less inflammatory reaction and coagulation of the folds of the tubal mucosa than does either plain catgut or bone wax. It is also evident that the closest approach to the normal unoperated appearance of the tube is obtained by the use of allantoic membrane within the lumen. Section 5(D) shows that the amount of scar tissue produced as a result of the end-to-end anastomosis is not excessive and probably would not offer any appreciable obstruction to the passage of an ovum, since there is so little relative decrease in the tubal lumen.

### CONCLUSIONS

All operations in which these two procedures were carried out resulted in tubal patency, with few if any adhesions about the field of operation.

However, evaluation of this technique is difficult on the basis of the work here reported, for it has been carried out, with few exceptions, upon the normal tubes of *Macacus rhesus* monkeys. While this allowed of more critical examination of the physical results than would have been possible in the human being, it must be borne in mind that many observers have come to grief through predicating human reaction upon animal experimentation. While realizing fully then that the diseased human Fallopian tube presents a number of barriers to success that are not encountered in experimental animals, it is believed that the procedure described above will result in far better end results than those which have previously been reported.

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### DISCUSSION

DR. FREDERICK C. HOLDEN.—During my early days at Bellevue Hospital, we tried many procedures for the purpose of conserving menstrual function when operating for pelvic inflammatory disease. We found the Estes operation to be most satisfactory in cases when bilateral salpingectomy and partial oophorectomy were indicated. It is technically easy to learn and gives good physiologic results.

DR. I. C. RUBIN.—My personal experiences with ovarian implantation have not been successful. I have done the Estes operation on two patients and have done several implantations of the ovary by the Touffier method. I have had one doubtful pregnancy following the introduction of one of the poles of an ovary into the uterine cavity, ending in abortion. That, of course, I do not consider a successful case.

Dr. Gepfert's contribution is extremely ingenious. What it is going to turn out to be is difficult to say. He was dealing with practically normal tubes in a monkey whose rehabilitative and regenerative powers and resistance are far greater than those which any human female possesses. There is, besides, the factor of the pathologic situation which we meet with in the human subject. Dr. Gepfert has however shown that the allantoic membrane is valuable for the purpose of keeping the ostium or new stoma patent.

I would like to suggest that for the test of tubal patency in the monkey, which I think is important, he can employ the clinical method of insufflation if he will simply split the cervix laterally and so dispose of the obstruction offered by the

Fig. 4(B) is a cross section of a similar tube six weeks after the introduction of bone wax into the tubal lumen. It will be noted that a considerable portion of the bone wax is still present.

Fig. 4(C) is a cross section of a similar tube six weeks after the introduction of plain catgut.

Fig. 4(D) is a cross section of a similar tube six weeks after the introduction of chromic catgut.

Fig. 5(A) is a cross section of a similar tube six weeks following operation and the introduction of chromicized allantoic membrane.

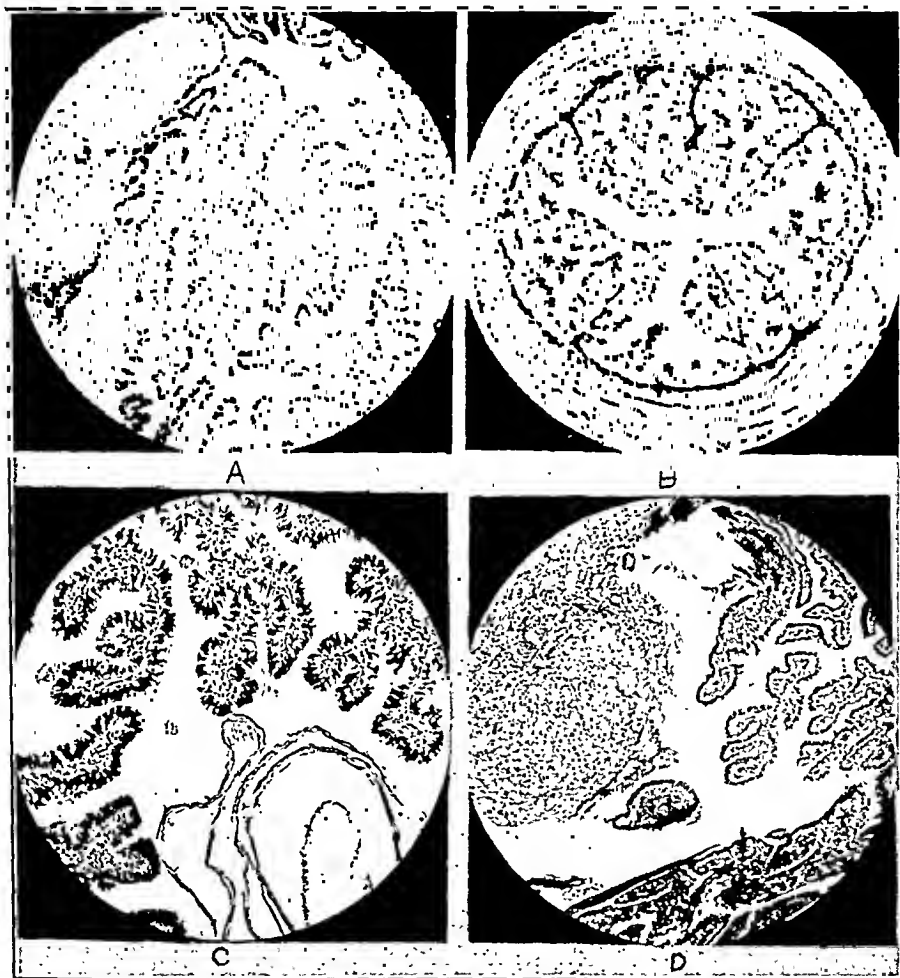


Fig. 5.—(A) Tube of *Macacus rhesus* monkey six weeks after introduction of allantoic membrane. (B) Similar tube after eighteen days. (Low power.) (C) Similar tube after fourteen days, showing allantoic membrane in lumen. (High power.) (D) Site of end-to-end anastomosis, six weeks after operation. (High power.)

Fig. 5(B) is a cross section of a similar tube eighteen days after the introduction of allantoic membrane.

Fig. 5(C) is a cross section of a similar tube fourteen days after operation and the introduction of allantoic membrane. This section demonstrates clearly the lack of inflammatory reaction to the allantoic membrane which may be seen to be still present in the tubal lumen.

Fig. 5(D) is a longitudinal section cut through the point of anastomosis in a similar tube, which had been subjected to an end-to-end anastomosis six weeks previous to removal of the tube.

recently. The operation itself is not difficult but is, of course, time consuming. The use of small instruments is absolutely essential.

For those who are interested I may say that the allantoic membrane is made by Lewis and Co., manufacturers of Curity catgut. It is contained in tubes and is obtainable in sheets 3 by 4, 4 by 6, and 6 by 8 inches in size. They have two products: one is plain and the other is chromicized. I strongly advise against the use of the unchromicized product because it produces a much more marked inflammatory reaction than does the chromicized.

## THE TREATMENT OF DYSMENORRHEA WITH TESTOSTERONE PROPIONATE\*

### THE BIOLOGIC EFFECTS OF TESTOSTERONE PROPIONATE IN THE SEXUALLY MATURE WOMAN

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THE subject of dysmenorrhea has engaged the attention of numerous investigators and an extensive literature has accumulated on the subject. The etiology of this distressing condition, however, is still obscure and its treatment still unsatisfactory. Reviews of the various hormonal theories of the cause of dysmenorrhea have recently been published by several authors.<sup>1-4</sup> Briefly, there are three current theories as regards the etiology of dysmenorrhea: (a) Deficiency in progesterone, permitting of the unopposed action of estrogenic hormone upon the uterine muscle; (b) excessive estrogen production resulting in hypermotility of the uterine musculature; and (c) excessive progesterone activity.<sup>5</sup> None of these theories is, however, adequately supported by controlled experimental studies.

The present communication deals with the treatment of dysmenorrhea with male hormone (testosterone propionate). The rationale for this form of therapy is based on the observation that testosterone counteracts certain of the physiologic effects of the estrogens in animals and human beings.

Ihrke and D'Amour<sup>6</sup> have shown that extracts of bull testes suppress estrus in rats. Similar results were obtained with testosterone by Robson<sup>7</sup> in mice and Brown<sup>8</sup> in rats. Zuckerman<sup>9</sup> has shown that in monkeys testosterone propionate inhibits follicle maturation and luteinization, resulting in suppression of the menses. Hartman<sup>10</sup> reported somewhat similar observations in monkeys. Recent experimental studies with testosterone in human females indicate that testosterone, if given in adequate dosage, suppresses the characteristic progesterone effect in the premenstrual endometrium and inhibits the usual proliferative phenomena so that the endometrium is reduced to a state of hypoplasia or atrophy;<sup>11</sup> causes regression in the vaginal smear<sup>12, 13</sup> and diminution of the glycogen content of the desquamated epithelial cells to a degree witnessed only in advanced estrogen deficiency (postmenopause or castration);<sup>13</sup> suppresses menstruation<sup>11-14, 27</sup> and inhibits the contractions of the uterus in rabbits<sup>15, 16</sup> and of the Fallopian tubes in women.<sup>17</sup>

\*Read at a meeting of the New York Obstetrical Society, December 13, 1938.

†Joseph Brettauer Fellow in Gynecology.

colliculus, a method which Dr. Morse and I have reported. I think he will get information more in that way than by resorting to the needle puncture of the uterus to insufflate the tubes.

DR. FRANCIS W. SOVAK.—There are one or two points that I want to discuss in connection with Dr. Geffert's presentation: First, it is very unusual to meet with an obstruction at the site Dr. Geffert has worked on. If you have an obstruction 2 or 3 cm. from the cornual portion of the tube, you are almost certain to have one also in the interstitial portion. Second, it is known to all of us that for reconstruction of a long, narrow viscus an end-to-end anastomosis is rather difficult and is likely to leave partial obstruction due to scar tissue.

I think he is wrong in stating that we are shortening the tube by the implantation operations. We have all seen inflamed tubes which are much longer than the normal tubes. In one case where pregnancy followed bilateral implantation, I was able at a subsequent operation to visualize the operative field and found that these tubes were not much shorter than the normal ones. I think that the allantoic membrane for the fimbriated extremity in association with the cuff operation will prove of value.

DR. BENJAMIN P. WATSON.—It has always seemed to me that the Estes is a bad operation. It has been difficult for me to conceive how an ovum, liberated from the ovary directly into the uterine cavity and there presumably immediately fertilized, can ever be implanted in the uterus. The ovum usually is fertilized at the outer end of the tube and it undergoes its first development during the passage down the tube into the uterus and it can only become implanted into the uterus after it has reached that stage of development. It, therefore, seems to me a very extraordinary thing if an ovum fertilized in the uterine cavity can stay there long enough, those necessary six or seven days, before it actually implants there.

The other objection, of course, is that only a very small pole of the ovary can possibly discharge an ovum into the uterus and the follicle that is ripening may be altogether distant from that small point of entry into the uterus. Consequently, it seems to me that the solution of this problem must lie in a proper reconstruction of a tube and of a tube of sufficient length to permit time for the ovum to develop during its passage down before coming into the uterus.

DR. WILLIAM H. CARY.—I recall that in 1927 I had occasion to review all the literature on this subject. If my recollection is correct, there was an unfortunately large number of complications following Estes' work, and I think Dr. Geffert has said that the percentage of successes is 2.4. Is that correct?

DR. FRANCIS W. SOVAK.—In answer to Dr. Watson may I report actual experiences. When we first attempted the modification of the Estes operation with the use of our reamer, we had six bilateral cases. Of those six, 4 became pregnant. Three of the patients subjected themselves to an induced abortion for economic reasons, but we recovered the products of gestation on the ward. The fourth patient aborted spontaneously and in her case we also recovered the products of gestation.

DR. GEFFERT (closing).—There were 2.2 per cent successful deliveries, but 4.4 per cent of pregnancies. Some recent work shows that the use of certain endocrine substances stimulates regeneration of the tubal mucosa. By using these substances, we hope to obtain a complete regeneration of the tubal mucosa before the allantoic membrane has been absorbed. This may eliminate a large part of the scar tissue resulting from the end-to-end anastomosis.

The source of the allantoic membrane is interesting. As the cow approaches term, the allantois, a sac between the amnion and the chorion, contains from 8 to 16½ liters of fluid, and is a prolific source of allantoic membrane for the purposes we have described here.

Although the report today was on experimental work, we have done four human cases. The postoperative results are not known, due to the fact that all were done



some of the cases injections were given throughout the entire month, in several, only during the first week of the cycle and, in others, treatment was started on the fifteenth or sixteenth day of the cycle and continued up to the onset of the following menstrual period. The majority of the patients were treated during 3 successive cycles. The dosage of testosterone propionate was varied in different cases from 50 to 900 mg. per month. The total dosage varied from 100 to 1,500 mg. This wide variation in the amount of hormone administered occurred because of the uncertainty, in the early part of the investigation, as to the optimal dosage.

TABLE I

*Results of Treatment of 30 Cases*

Satisfactory results	26 cases
Complete relief	22 cases
Incomplete relief	4 cases
Failures	4 cases

*Follow-Up on 25 Cases*

Symptom-free from 3 to 24 months after cessation of treatment	14 cases
Slight recurrence of pain after 2 months	8 cases

## RESULTS

Satisfactory clinical results occurred during the course of treatment in 26 of the 30 cases (Table I). Twenty-two cases had complete relief; 4 were considerably improved; and in 4 cases there was no improvement. Following the discontinuation of treatment, 17 patients remained symptom-free during the period of observation which varied from three to twenty-four months. Ten of these have been observed for more than six months. In 8 cases there was slight recurrence of the pain within two months after discontinuation of the testosterone. In one patient there was a complete recurrence of the pain one month after the last injection.

In 9 cases 1 or 2 menstrual periods were suppressed during the course of treatment. Subsequent periods occurred with customary regularity. It is interesting to note that the menstrual bleeding which occurred in the menorrhagia group was appreciably reduced. A slight but definite decrease in the amount of bleeding occurred also in 10 patients of the normally menstruating group during the course of treatment. In 2 cases during the course of treatment, menstruation occurred five and ten days early. After discontinuation of the testosterone, a regular cycle was established.

## ANALYSIS OF THE FAILURES

Of the 4 patients who failed to respond to the testosterone, 1 had uterine myomas; 1 probably had chronic adnexitis; the remaining 2 exhibited no palpable signs of pelvic disease. The dosage of testosterone used in these cases was comparable to that given the successful cases. That the failure to relieve the pain was not due to insufficient testosterone was indicated by the fact that in 3 of the patients a menstrual period was suppressed and in the remaining one delayed. All of these patients exhibited regressive changes in the vaginal smears. The failure in 2 cases may possibly be explained by the presence of organic disease.

## ENDOMETRIAL BIOPSY STUDIES

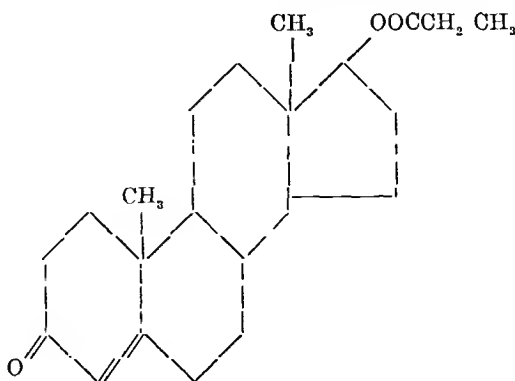
In all of the 12 cases in which premenstrual biopsies were taken before treatment was begun, a secretory endometrium was found (Fig. 1). In 6 cases, endometrial biopsies were obtained during and after the course of treatment. The number of endometrial biopsies obtained in each case varied from 2 to 6. The endometrial biopsies obtained after testosterone administration, in all of these cases, revealed an absence of the secretory phase (Fig. 2), indicating a suppression or inactivation of progesterone. In addition, the endometrium in some cases showed some degree of hypoplasia, indicative of diminished estrogen effect (Fig. 3). Endometrial biopsies

All of these phenomena indicate an antagonism between the female sex hormones (estrogens) and the male hormones (androgens). Furthermore, it has been known for some time that androgens are excreted in the urine by normal mature women. The role of the male hormones in the endocrine metabolism of the female assumes further significance in the light of the recent androgen studies reported by Koeh and his co-workers.<sup>18, 19</sup> These studies have shown that normal, young women excrete daily an average of 26 international units of androgenic substance, as compared with an average of 40 units per day by men of similar age. It is noteworthy also that only traces of androgenic hormone (0.8 to 2.0 international units per liter) are excreted by girls before puberty. These observations warrant the assumption that androgens are intimately involved in the cyclical phenomena associated with normal menstruation. This suggested the possibility that dysmenorrhea might be due to an androgen deficiency resulting in the unopposed action of the ovarian hormones; and led to the use of an androgenic hormone (testosterone propionate) in the treatment of dysmenorrhea.

#### PROCEDURE

The present study was conducted on a series of 30 patients, whose ages varied from 15 to 45 years. Seventeen patients were under 30 years of age; 10 patients between 30 and 40; 3 patients were over 40 years of age. In all but 5 cases, the dysmenorrhea had been present since puberty. Twenty-seven of the patients had no palpable evidence of pelvic disease; 2 had suggestive signs of chronic adnexitis; one had several small myomas. Nineteen of the patients had normal, regular menstrual cycles; 11 had various degrees of menorrhagia.

In order to determine the presence or absence of normal progesterone activity and also to evaluate objectively the effect of the administered hormone, endometrial biopsies and vaginal smear studies were performed prior to and during the course of treatment. The endometrial biopsies were obtained with a suction curette. Vaginal smears were prepared according to the technique previously described.<sup>20</sup> The androgen selected for this study was crystalline testosterone propionate\* (oreton, Schering; perandren, Ciba) which has been shown to be the most effective male hormone preparation.<sup>21</sup> The structural formula of testosterone propionate is:



#### DOSAGE

The testosterone propionate was administered intramuscularly in the gluteal region 3 times weekly in individual doses of 10 to 50 mg. per c.c. of sesame oil. In

\*For the testosterone propionate used in this investigation, we are indebted to Drs. Stragnell, Schwenk and Gilbert of the Schering Corporation, Bloomfield, N. J. and to Mr. R. Mautner of Ciba Pharmaceutical Products, Summit, N. J.

of squamous epithelial cells and the disappearance of the leucocytes and small atrophy cells (Fig. 6). In 7 cases in which the dysmenorrhea was relieved, the smears did not exhibit any evidence of regression either during the course of treatment or during the following month. Apparently a satisfactory clinical result can be achieved with doses of testosterone propionate that are smaller than are required to produce the regressive changes in the vaginal smears.

#### SIDE EFFECTS OF TESTOSTERONE PROPIONATE

Testosterone propionate in some cases produced masculinizing effects which are worthy of note, viz., facial hirsutism (6 cases); hoarseness of the voice (8 cases); very slight enlargement of the clitoris (2 cases); atrophic vaginitis (4 cases). The hirsutism, for the most part, is confined to the upper lip and chin and consists of a

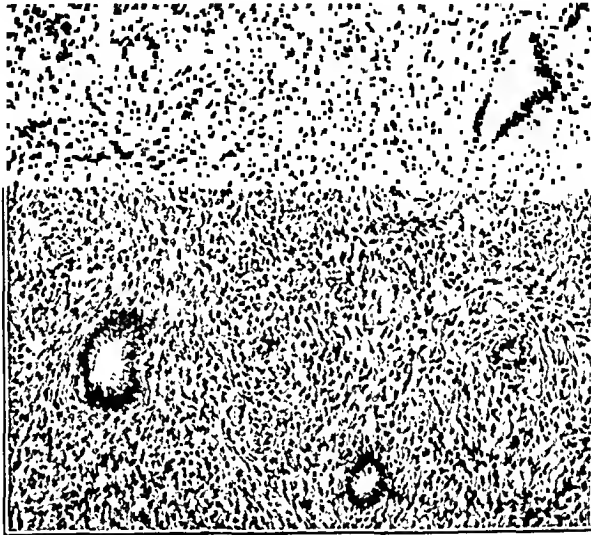


Fig. 3.—Case H. L. Endometrial biopsy after 800 mg. testosterone propionate given over a period of six weeks. Menstrual period suppressed. Biopsy taken two weeks after date of expected period. Note marked hypoplasia of the endometrium.

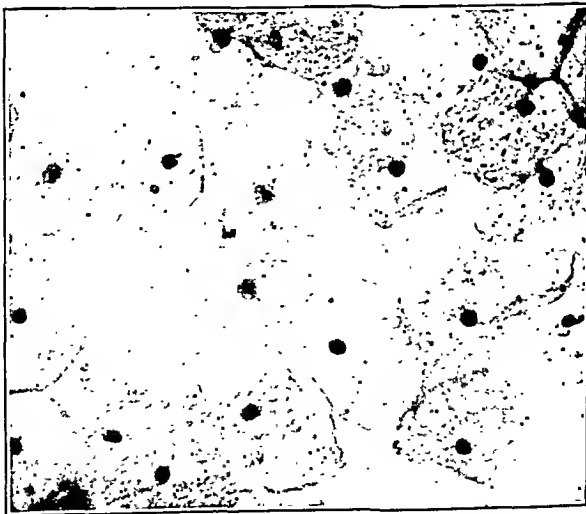


Fig. 4.—Case N. F., aged twenty-five years, gravida 0. Smear taken ten days premenstrually showing full estrogen effect (Reaction IV).

performed before the next period (3 to 5 weeks after discontinuation of treatment) revealed normal secretory changes, indicating a restoration of a normal estrogen-progesterone relationship. In these cases the dosage of testosterone propionate varied from 500 to 900 mg.



Fig. 1.—Case H. L., aged twenty-four years, gravida i, para i. Premenstrual biopsy (taken before testosterone propionate), showing secretory endometrium. Menstruation began six days later with severe pain.

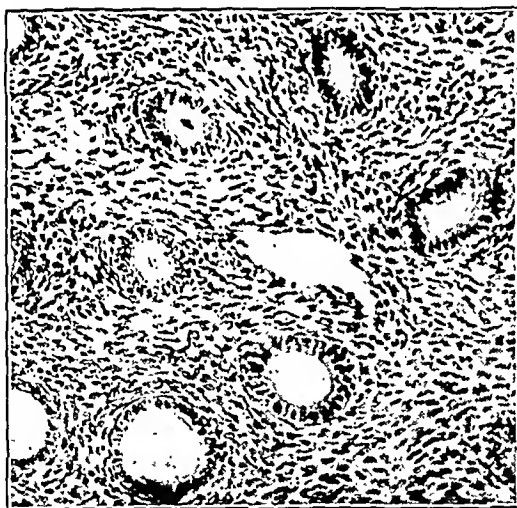


Fig. 2.—Case H. L. Premenstrual endometrial biopsy after 225 mg. testosterone propionate had been given during the preceding twenty-six days. Note absence of secretory phase. Uterine bleeding began the following day, lasting six days without pain.

#### VAGINAL SMEAR STUDIES

Smear studies were done in 24 cases. Preliminary smear studies revealed normal estrogen effect in all (Fig. 4). Following the administration of testosterone propionate, some cases showed regressive changes in the vaginal smears, as indicated by the appearance of variable numbers of "atrophy cells" and leucocytes (Fig. 4). The dosage administered to these cases manifesting regressive changes varied from 350 to 900 mg. of testosterone propionate. The smears remained in the regressive stage (estrogen deficiency) for periods varying from one to three weeks and thereafter showed signs of gradual recovery manifested by the return of large numbers

activity. In the cases in which the vaginitis was bothersome, relief was obtained in a few days by the nightly use of vaginal suppositories containing 2,500 rat units of estradiol (prognon-DH).

#### DISCUSSION

The biologic effects of testosterone propionate in the sexually mature woman vary, depending upon the dosage as well as the time of the cycle when the hormone is administered. There appears, furthermore, to be considerable individual variation in the response to similar doses of testosterone. With doses of 200 mg. or less, menstruation was not affected (with the exception of 2 patients in whom menstruation occurred prematurely, five and ten days) and no objective changes were noted in either the endometrium or the vaginal smears. Three hundred milligrams or more given during the first ten days of the cycle may cause delay (from three to five days), diminution in the flow of the next period, and may suppress the normal progestational changes in the endometrium. Approximately similar doses given during the last 10 days of the cycle usually cause no delay in the period and no endometrial and vaginal smear changes during the current cycle.

If doses of 500 mg. or more are given during the first seven to ten days of the cycle, the next menstrual period may be delayed from two to six weeks. During the period of amenorrhea the endometrium shows absence of the secretory phase and various stages of subnormal proliferation. Premenstrual biopsies performed during succeeding cycles show a normal secretory endometrium. The vaginal smears during this period of temporary amenorrhea in all cases show advanced degrees of estrogen deficiency indicated by the predominance of leucocytes and atrophy cells with absence of cornified cells (Reaction I and II). In all of these cases evidence of return to a normal estrogen effect (disappearance of leucocytes and replacement of atrophy cells by squamous epithelial cells) was noted two to three weeks after the discontinuation of testosterone propionate.

It is apparent that striking undesirable effects, both clinical as well as morphologic, result from administering more than 500 mg. of testosterone propionate. This appears to be the approximate threshold of androgen tolerance in the human female. Fortunately, one can achieve satisfactory therapeutic results with smaller doses without inducing any of the undesirable effects noted above and without incurring any danger of subsequent interference with the normal menstrual phenomena.

It is interesting to note that one patient (not included in this series) missed a period after 600 mg. of testosterone propionate, developed a "negative" smear which persisted for two weeks, then began to return to normal. At the same time she developed slight hoarseness and facial hirsutes which gradually subsided. When the patient did not menstruate the following month, a pregnancy test was performed which was found to be positive. The patient had apparently conceived during the period of amenorrhea. She was delivered at term of a perfectly normal male baby, weighing 7 pounds 12 ounces.

fine, downy growth. Brunettes with a natural tendency to hirsutism seem to be more susceptible. There is a gradual disappearance of the hair growth after discontinuation of the testosterone. In 4 of these cases the growth disappeared completely at the end of three months; in 2 cases a slight growth was still present at the end of four months. The hoarseness of the voice occurred before the hirsutism in 6 cases in which both were present. The patients usually attributed the changes in the quality of the voice to a cold. Examination of the larynx revealed diffuse congestion of the vocal cords. Following cessation of testosterone administration, improvement occurs progressively but slowly. At the end of six months there was still some slight hoarseness noticeable. In all of the patients in whom these effects were produced, the dosage exceeded 500 mg.

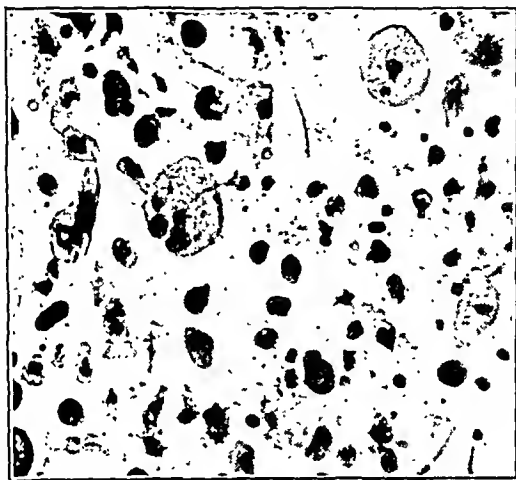


Fig. 5.—Case N. F. Smear showing marked estrogen deficiency (Reaction II) after 650 mg. testosterone propionate. Menstrual period suppressed. Smear was taken two weeks after date of expected period. Note "anisocytosis" and "poikilocytosis"; predominance of small epithelial cells ("atrophy cells"); scattering of leucocytes.



Fig. 6.—Case N. F. Smear taken twenty-six days after smear in Fig. 5. Note return of squamous epithelial cells; disappearance of "atrophy cells" and leucocytes. Definite estrogenic effect (Reaction III). Patient menstruated sixteen days later without pain.

Four of the patients complained of vaginal discharge which was found to be due to a vaginitis analogous to the senile type. Vaginal smears revealed the characteristics of advanced estrogen deficiency. The vaginitis subsides spontaneously within two to three weeks and is associated with a replacement of the "atrophy cells" in the smears by the large squamous epithelial cells, indicative of return of estrogen

similar amounts of testosterone given during the last week of the cycle (after ovulation has occurred) have no effect on the following menstrual period. This theory, however, does not explain the rapid appearance of morphologic signs of advanced estrogen deficiency in the endometrium and vaginal smears following testosterone administration, since it is inconceivable that suppression of estrogen formation alone during one cycle would, by itself, be the cause of such striking regressive histologic changes. Signs of marked estrogen deficiency (Reaction I and II) were found as early as three weeks after testosterone was administered, whereas after surgical castration evidence of similar degrees of estrogen deprivation is not usually observed until many months have elapsed after removal of the ovaries. The rapidity with which such an advanced degree of histologic regression in the vaginal mucosa makes its appearance suggests that it is not solely the result of cessation of estrogen production but indicates that in addition there is also an actual inactivation of whatever estrogens are stored or circulating in the body.

It is tempting, in the light of the observed biologic effect of testosterone in women, to formulate a theory concerning the causation of functional dysmenorrhea. According to this theory, the androgens are conceived as playing an important role in the hormonal organization of the normally menstruating female, viz., to balance or modify the physiologic effects of the ovarian hormones. Dysmenorrhea is attributed to an androgen deficiency resulting in the unopposed or unmodified action of the ovarian hormones. The following evidence is offered in support of this theory: (a) androgens play an important part in the normal hormonal economy of the sexually mature female; (b) there is experimental evidence indicating a definite antagonism in the human female between estrogens and androgens; (c) 86 per cent of the cases of functional dysmenorrhea in this series were relieved when treated with a potent androgen (testosterone propionate). This theory awaits verification by quantitative studies of the androgen excretion in cases of functional dysmenorrhea.

The question arises as to the practical therapeutic value of testosterone propionate for functional dysmenorrhea. We realize that an accurate evaluation of clinical results in as complex a condition as dysmenorrhea is beset with difficulties. It is well-nigh impossible to exclude a psychic component from the therapeutic results obtained regardless of what form of therapy is employed. However, in this study an attempt was made, by the correlation of objective findings with the clinical results, to evaluate the therapeutic effect of the administered hormone per se. Although the results in this series have been very gratifying, we do not believe that testosterone is the complete answer to the problem of dysmenorrhea. We do feel, however, that testosterone is a valuable addition to our therapeutic armamentarium.

#### SUMMARY AND CONCLUSIONS

1. A group of 30 patients with dysmenorrhea was treated with testosterone propionate.

We feel that the optimal dosage for the relief of dysmenorrhea is in the neighborhood of 250 to 350 mg. given in divided doses during one cycle. If the pain is relieved completely or partially with this dosage, it is advisable to give an additional course of therapy decreasing the amount by half. If only slight or no improvement is obtained, a second course should be given.

We have found that the vaginal smear serves as a sensitive indicator of androgen overdosage. Regressive changes in the smear occur several weeks before the clinical manifestations of androgen overdosage appear. Although we have not observed any of the undesirable androgenic effects with the dosage recommended, we wish to draw attention to the fact that there is some variation in the tolerance of different individuals to the hormone and suggest that vaginal smears be taken twice weekly to guard against the occurrence of the undesirable side effects in patients with subnormal tolerance. If the vaginal smears show evidence of estrogen deficiency (Reaction I or II), therapy should be discontinued. It is worthy of note that in many of the cases symptomatic relief was obtained with doses which were insufficient to produce regressive changes in the smears. In 4 cases symptomatic relief was obtained with less than 100 mg. The follow-up in these cases varied from four to sixteen months without recurrence of symptoms.

As we survey the results of this investigation, the question arises as to the *modus operandi* of the testosterone. The results of the present study seem to indicate that in the sexually mature human female testosterone propionate suppresses or counteracts the effects of the ovarian hormones (estrogen and progesterone). This is in agreement with the reports of suppression of estrus in animals following male hormone administration.<sup>6-10</sup> It should be pointed out, however, that recent studies have shown that testosterone propionate has a definite gonadotropic effect in immature female rats, resulting in follicle growth, corpora lutea formation and hypertrophy of the uterus and vagina.<sup>22</sup> The trophic effects on the uterus and vagina can be produced in spayed (as well as intact) both immature and mature rats.<sup>23-25</sup> These observations appear to indicate that in rats testosterone propionate has a gonadotropic effect (produced, probably, through the hypophysis) as well as a direct estrogen-like effect (demonstrated histologically) on the genital tract. In human beings and monkeys, on the contrary, the testosterone evidently has an inhibitory action opposing or negating the effect of the ovarian hormones. It is interesting, in this connection, to note that it has been shown that testosterone propionate suppresses the excessive gonadotropic hormone excretion in a human female castrate<sup>26</sup> and it seems not illogical to assume that a similar inhibition of the gonadotropic activity of the hypophysis may occur in women with regular menstrual cycles. This concept of the inhibitory action of testosterone upon the hypophysis is supported by the observation that administration of adequate amounts of testosterone propionate during the first week of the menstrual cycle (before the gonadotropic factors of the hypophysis have exerted their effect on the ovaries) results in suppression of the subsequent menstrual period, whereas



## DISCUSSION

DR. SAMUEL H. GEIST.—This contribution represents a step in the investigation of the value of androgen therapy in functional gynecologic disease. We have already published some observations on the use of this agent in the treatment of certain types of metrorrhagia and menorrhagia where we obtained what we believe to be very suggestive and in some instances very satisfactory results.

In view of the fact that the normal woman excretes a definite amount of male hormone we cannot disregard its importance in her physiologic make-up. We feel that an investigation of the value of androgens in various types of endocrine diseases in the female might produce very helpful results in certain functional conditions that have been difficult to treat. They include metrorrhagia and menorrhagia and dysmenorrhea, and also some aspects of the menopause itself. Recently there have been some publications by French authors on the treatment of fibroids on an endocrinologic basis, with some very suggestive results.

The failures which we reported are in keeping with the treatment of dysmenorrhea by any method. They may be due to the fact that our dosage is insufficient. They may be due to the fact that the individual is resistant to the dose which we considered adequate, and what is much more important, they may be due to the fact that we used it in some cases of dysmenorrhea where there was no indication for its use.

Dysmenorrhea does not represent a single entity. On the contrary, it is a symptom-complex which often is associated with many etiologic factors and until we learn to classify it properly and recognize the various types there will naturally be a certain proportion of failures with any single method of treatment. We, of course, realize that the number of cases in this study is small and consequently definite conclusions cannot be drawn from them. We do not offer this form of therapy as a cure-all, but we think it is a very suggestive line of thought and a very encouraging line of therapy.

DR. HOWARD C. TAYLOR, JR.—This paper must be considered from two separate points of view: first, as a contribution to the physiology of the female reproductive system, and, second, as a possibly practical method of treating dysmenorrhea. From the first point of view the paper is unquestionably important. From the second, as is the case with all new contributions in the treatment of dysmenorrhea, one should withhold severe judgment.

From a pathologic standpoint this paper brings out certain points. In the first place, it corroborates experimental work in animals, showing that testosterone may prevent the effect of estrogenic and progestational substances on the endometrium and on the vagina, as indicated by the changes in the character of the endometrium and the vaginal smear. In the second place, testosterone is seen to have the ability in large enough doses to bring out the masculine qualities, such as changes in the voice, changes in the clitoris and the development of abnormal hair.

An important point which this paper seems to settle is the range of dosage that we will probably have to use when testosterone is administered. This is of fundamental value. The treatment with estrogenic hormone went through a period of years when the dosage was so small that there could have been no actual effect although we imagined the contrary. We may hope to skip this stage with testosterone, for we start with this report in which the substance has been given until it produced objective effects. We have been told that with less than 200 mg. menstruation is unaffected, while with a dosage of over 250 mg. there may be a temporary atrophy of the endometrium. In doses of over 500 mg. there may be some unlooked for results, such as masculinizing effects. The fact of having a dosage related to objective effects is going to be of great assistance to us in working out the therapy of this new drug.

As far as the practical application of this method to the treatment of dysmenorrhea is concerned one can raise certain questions. Any type of therapy will be followed by a certain percentage of cures in dysmenorrhea. Wilson presented before this Society a few days ago a paper on the treatment of dysmenorrhea with

2. The biologic effects, clinical as well as morphologic, of testosterone propionate on the sexually mature human female are described.

3. The level of testosterone tolerance was established at approximately 500 mg.

4. Administration of upwards of 500 mg. resulted in the appearance, in some of the cases, of: (a) masculinization phenomena, viz., hoarseness of the voice, facial hirsutes, slight enlargement of the clitoris; and (b) evidence of estrogen deficiency, viz., suppression of menstruation, atrophic vaginitis, varying degrees of hypoplasia of the endometrium, and "negative" vaginal smears.

5. Normal cyclical phenomena (clinical and morphologic) returned spontaneously in all cases within two months after treatment.

6. With doses of 300 mg. or less neither androgenic nor estrogen deficiency effects were produced.

7. In the treatment of dysmenorrhea the dosage of testosterone propionate recommended is 250 to 350 mg. given during one cycle.

8. Symptomatic relief was achieved in 26 of the 30 cases.

9. The suggestion is made that the biologic effects of testosterone propionate (in doses of 500 mg. or more) in women is brought about by inhibition of the gonadotropic factors of the hypophysis with consequent suppression of ovulation, estrogen and progesterone formation and menstruation, as well as by inactivation of the circulating estrogens and estrogen stores in the body.

10. The therapeutic effects noted with smaller doses of testosterone propionate are probably the result of partial inactivation or modification of the action of the estrogens and progesterone.

11. The theory is advanced that functional dysmenorrhea may be caused by an androgen deficiency.

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DR. SALMON (closing).—I should like to point out that in this presentation two separate groups of facts are incorporated: (1) an attempt to determine the effect of testosterone on the adult, human female and (2) the effect of testosterone on functional dysmenorrhea. In order to determine the first, we experimented with dosages varying from 50 to 900 mg. per month. In our report, we have deliberately stressed the masculinization phenomena and the estrogen neutralizing effects of testosterone because they exemplified, in an exaggerated manner, the probable physiologic significance of androgens in the human female. Fortunately, it appears that there is a wide margin of safety between the therapeutic dose and the dosage required to produce estrogen deficiency symptoms or androgenic effects.

The problem of the mechanism of testosterone action in women is an intriguing and, in some of its aspects, at present, a baffling one. That inhibition of the gonadotropic activity of the hypophysis and consequent suppression of ovulation and menstruation occur as a result of administration of large doses of testosterone propionate seems proved. But what do we know about the mechanism of the masculinization phenomena? It seems that the testosterone, after inhibiting the hypophysis and inactivating the circulating estrogens or estrogen stores, stimulates some growth of hair on the face and coarsens the voice. Whether the testosterone produces these masculinizing effects directly or through the adrenal cortex is not clear. It seems likely, however, that the former is the more probable *modus operandi*. It is interesting, in this connection, to recall that Butler and Marrian recently isolated isoandrosterone (an androgen not far removed from testosterone) from the urine of a woman with adrenal virilism.

But what happens when doses that are too small to cause masculinizing effects or suppress menstruation are given? We suggest that in the normal mature female there is a balance between the androgens on the one hand and the estrogens and progesterone on the other and that when testosterone is given in dysmenorrhea it partially inactivates or, rather, modifies the action of the estrogens and progesterone. Our observation that not only functional dysmenorrhea but also some types of functional bleeding, premenstrual tension and premenstrual mastalgia can be relieved with testosterone propionate, suggests that in these conditions, too, the normal balance is upset because of a deficiency or abnormality in the androgen metabolism. I trust, however, that we have not created the impression that we have conclusive evidence to support this theory. Our evidence, I must confess, is entirely indirect, based on the changes in the vaginal smears and endometrium and on clinical observations. We are fully aware of the necessity of following these cases with androgen, estrogen, and pregnandiol excretion studies before we can prove our theory of androgen deficiency in functional dysmenorrhea.

If we look to animal experimentation for confirmation of our theory, we are met with a confusing array of paradoxical phenomena. As a matter of fact, some animal experiments indicate that testosterone actually has a stimulating effect on the genital tract, in some respects similar to that of the estrogens. Thus, if testosterone is given to immature, female rats, it produces opening of the vagina within seventy-two hours, follicle growth and corpora lutea in the ovaries, hypertrophy of the uterus and proliferation of the endometrium. The effects on the uterus and vagina occur in spayed, immature rats as well, indicating that the testosterone has a direct estrinlike effect on the Müllerian tract of rats as well as a gonadotropic effect upon the immature ovaries, the latter effect exercised through the hypophysis. Coincidentally, the preputial glands, which are the homologues of the prostate, are stimulated to a five- to eight-fold increase in size. We find, therefore, that giving male hormone to immature female rats produces not only precocious development of all the components of the female genital tract but also stimulates the vestigial male organs. With the present status of our knowledge, animal experimentation does not help us in our quest for an understanding of the mechanism of the testosterone action in the human female. We must content ourselves, for the time being, with the knowledge that testosterone is very closely related, chemically, to progesterone and corticosterone; that under normal conditions a significant amount of androgenic hormone is excreted by the adult female; that androgens probably play an important role in the metabolism of the steroid sex hormones of the human female; that

progesterone and reported a fair percentage of cures, using somewhere between 2/25 and 6/25 of a rabbit unit. There have been numerous other reports in the literature in the last few years, of cure of dysmenorrhea with various types of endocrine therapy. One report (Lackner, Krohn and Soskin, *AM. J. OBST. & GYNEC.* 34: 248, 1937) showed 20 per cent of failures and another (Katz and Parker, *AM. J. OBST. & GYNEC.* 34: 38, 1937) only 2 per cent. This report which indicates 88 per cent of successes is excellent but it must bear the burden of contrast with previously undoubtedly over-optimistic figures.

The second point is the question whether these are temporary or permanent results. The cases have been observed over a relatively short period of time. It would be a most unexpected piece of good fortune, if the unwanted side effects, such as atrophy of the endometrium and the occasional masculinizing signs, should be temporary and the beneficial effects, such as the disappearance of the pain, should be permanent.

There is, finally, one question which, although it is at present largely theoretical, is perhaps the most important one. One must ask whether with this substance in large doses we are not making too vigorous an assault on the fundamental physiology of the reproductive tract. It is to be remembered that in these doses one delays menstruation, one produces an endometrium which is said to be atrophic, one inhibits ovulation and in only double the therapeutic dose one produces certain masculinizing changes. To substitute for dysmenorrhea a type of endometrium which is atrophic is not the elimination of the specific cause of dysmenorrhea. It is simply a complete alteration, almost a cessation, of the functions of the reproductive tract. If you x-ray the pelvis and produce amenorrhea, you stop the pain of menstruation but do not eliminate the cause of the dysmenorrhea. There is at least the possibility then that this chemical attack on the function of the ovary may be as fundamental as the use of radiation. This treatment should be accepted with a certain degree of caution especially in young women who are still to bear their children. Testosterone in doses of 250 mg. is something a little different from what we have usually been accustomed to in gynecologic endocrinology, because it does involve such fundamental alterations in the physiology of the ovary and uterus.

These are not to be construed as criticisms, but merely as questions that come to one's mind at this time. I am anxious that they should not detract from what I believe is a very important addition to our knowledge of the physiology of the reproductive tract, and perhaps a very important contribution to our knowledge of the therapy of dysmenorrhea.

DR. ALFRED C. BECK.—A number of years ago in our clinic we attempted to suppress menstruation by x-ray in the treatment of certain cases of inflammatory disease. Perhaps the suppression of menstruation did eliminate some obscure inflammatory disease which was responsible for the dysmenorrhea. Instead of using the x-ray in some of these inflammatory conditions, the use of male hormone might be tried.

DR. ROBERT WALTER.—It is important to note that the undesirable side effects, i.e., hypertrichosis, voice changes, suppression of menses, etc., did not occur in this series of cases when 250 mg. or less of testosterone propionate were used. However, to guard against overdosage it is advisable to do vaginal smears simultaneously with the administration of testosterone propionate and to discontinue therapy when smears indicative of estrogen deficiency appear.

DR. HOWARD E. LINDEMAN.—The presenters of the paper have pointed out a masculinizing effect produced by the male hormone. As so many of these cases of dysmenorrhea in young women are associated with sterility, the question arises whether this tendency towards masculinizing, even though the androgen be given in small doses, would not still further diminish fertility. I would like to ask whether the authors of this paper have any knowledge of pregnancy following this treatment.

appendices removed through a McBurney incision when the true lesion, if exposure were adequate, would have been found in the pelvis.

Upon operation one finds many gradations of bleedings, from 10 c.c. of blood-tinged, straw-colored fluid to profuse intra-abdominal hemorrhage of a liter or more of blood. Occasionally the actively bleeding vessel may be seen, as was the case in one instance only of the series herein reported, but most often there is only a generalized oozing coming from the rupture site. Where the laceration is not extensive, removal of the clot with lock stitch closure of the defect, using fine catgut suture material, will control the hemorrhage. However, it may be necessary to remove the entire adnexa to control the bleeding. Additional indicated surgery such as appendectomy, cysto-oophorectomy, or suspension of the uterus, is permissible, depending on the patient's general condition.<sup>1</sup>

During the five-year period between 1932 and 1937, 35 cases of Graafian follicle or corpus luteum rupture have been collected from the surgical records of the City Hospital of Akron. The frequency with which this condition has been confused with acute appendicitis will be seen from Table I. Of these 35 patients, 30 were operated upon; none of which was correctly diagnosed preoperatively. Five patients with a clinical diagnosis of ruptured Graafian follicle were observed during 1936 and 1937 in the hospital, recovered, and were discharged without operation. One patient whose case history is abstracted below, had a ruptured right corpora lutea with active hemorrhage, intact left corpora lutea, and also incomplete intrauterine abortion. Of the 30 operated upon the preoperative diagnosis was appendicitis in 24 and ectopic pregnancy in six. Ruptured Graafian follicle occurred 18 times and ruptured corpus luteum 12 times. At the time of operation the offending ovary was found 20 times on the right and five times on the left side.

TABLE I. PREOPERATIVE DIAGNOSIS

APPENDICITIS		ECTOPIC PREGNANCY	
Acute	13	Right	2
Subacute	10	Left	4
Chronic	1		

The one outstanding symptom complained of with a marked degree of regularity was sudden pain; this occurred 30 times. In every instance it was located low down on either the right or the left side, and infrequently associated with nausea or vomiting. Weakness was recorded 12 times, and fainting twice. The pain which at first was said to be localized would later become diffuse and was intensified by motion, i.e., walking, bending, or stretching. In 24 instances the pain started on the right side. This probably accounts for the 24 preoperative diagnoses of appendicitis.

From the charts reviewed the physical examinations revealed various degrees of direct and rebound tenderness in one or the other lower quadrants. This tenderness was usually below McBurney's point.

condition occurs most frequently in females between 16 and 30 and very infrequently before the onset of menstruation or immediately before the menopause.<sup>3, 5, 7</sup> Nausea and vomiting occur but are not predominating symptoms of rupture of the ovary with hemorrhage. Leucocytosis and fever are found in both conditions. They are dependent, in rupture of the ovarian sexual apparatus, upon the reaction of the peritoneum to the foreign substance, i.e., follicular fluid or blood.

Rupture of the Graafian follicle usually occurs during the first three weeks of the menstrual cycle and most often between the twelfth and eighteenth days, whereas corpus luteum rupture occurs most frequently within the last week of the cycle or during the menses.<sup>3, 4, 7</sup> The history, therefore, is essential and the menstrual cycle should be carefully investigated. Patients sometimes give a history of onset associated with trauma, i.e., walking, strenuous exercise,<sup>8</sup> or a blow to the lower abdomen.<sup>9</sup> Many cases reported in the literature trace their onset to the sexual act.<sup>2, 10-12</sup> In the cases herein reported trauma was apparently not a predisposing factor.

On examination, if seen immediately after the accident, and if bleeding has been profuse, the patient may show signs of mild shock characterized by pallor, rapid pulse, and low blood pressure. Without a complete investigation one could easily confuse these findings with those frequently seen in ruptured ectopic pregnancy. If rupture is associated with slight hemorrhage, and if the right ovary is involved, the condition is usually confused with appendicitis. Examination of the abdomen will reveal palpable right rectus spasm, direct and rebound tenderness, however, with maximum tenderness somewhat below McBurney's point. Examination per vaginam because of the pain associated with manipulation of the internal genitalia causes one to suspect pelvic disease rather than appendicitis. In some instances slight enlargement of the ovary, or the presence of a definitely palpable mass, which is tender on manipulation, will focus one's attention on the internal genitalia rather than the appendix.

In mild hemorrhage there is no bulging of the cul-de-sac of Douglas such as is frequently encountered in ruptured ectopic pregnancy. The latter can be differentiated on the basis of missed periods, bleeding, early signs of pregnancy, and the appearance of a tender tubal mass. Where hemorrhage is fulminative it is not so important to differentiate as the exact cause preoperatively, for in any event operation is imperative.

The importance of a correct diagnosis is apparent when we realize that the patient, in whom rupture with mild hemorrhage occurs, is not necessarily a candidate for surgery whereas acute appendicitis or ectopic pregnancy is definitely a surgical problem. Brakely and Farr,<sup>13</sup> and Pratt,<sup>4</sup> state that in the mild cases, with rare exceptions, operative treatment is contraindicated. However, if the symptoms and signs do not subside and the correct diagnosis is still in doubt, operation is the procedure of choice. This decision is based on the premise of the grave danger associated with delay in acute appendicitis, and the minimal risk of an exploratory procedure. As stated by Meigs and Hoyt,<sup>3</sup> it is difficult to treat conservatively a patient who *might have* early acute appendicitis. In any event, if operation is decided upon the incision should be so placed as to give adequate visual exposure to the internal genitalia. There are doubtlessly some normal

Here we see that 9 cases of Graafian follicle rupture were associated with mild hemorrhage. The five patients with Graafian follicle rupture where the degree of hemorrhage was not recorded in the operative descriptions were operated upon through a McBurney incision. I assume that we should classify these in the category of slight hemorrhage. This would bring the group associated with less than 30 c.c. of blood loss up to 14. There were four cases of rupture of Graafian follicle with profuse hemorrhage; in each instance the entire involved ovary was removed. Of the 12 ruptured corpora lutea with hemorrhage, 5 were associated with moderate and 7 with profuse hemorrhage.

The McBurney incision was used 18 times, right rectus 6, and the midline 6 times. Nine ovaries, 4 tubes, and 30 appendices were removed. Of the 21 ovaries allowed to remain in situ, after recognition of the site of rupture, only 12 necessitated suturing to control the hemorrhage. In the remaining 9 involved ovaries bleeding had become quiescent and suturing was unnecessary. In no instance was a diagnosis of acute appendicitis made from the microscopic sections of the appendices removed.

#### ABSTRACTS OF CASE HISTORIES

CASE 1.—Mrs. C. H., a white female, aged 31 years, para ii, entered the hospital on Oct. 1, 1937 with a history of having missed her menstrual period in August. However, on September 14, she began having severe menstrual-like cramps, followed by slight vaginal bleeding. Three hours after the onset of pain and bleeding she began to hemorrhage and passed clots and some pieces of "flesh" which she identified as fetal membranes. Ever since this episode she has had dark brown vaginal discharge and irregular vaginal bleeding. Two days prior to her admission she had a sudden pain in the left lower quadrant which made her very weak; however, she did not faint. Following her attack of sudden pain there followed persistent soreness throughout her lower abdomen.

On physical examination the patient did not appear acutely ill. The abdomen was scaphoid, there was definite direct and rebound tenderness in the left lower quadrant. No mass could be palpated. Colostrum could be expressed from the breasts. Pelvic examination revealed some blackish vaginal discharge, and a patulous, multiparous cervix which felt soft. The uterus was slightly enlarged and soft. Motion of the cervix caused pain in the left adnexal region. The latter presented a small tender mass. There was no bulging of the cul-de-sac of Douglas. The laboratory findings revealed a white blood count of 7,100, 82 per cent neutrophiles, red blood count 3.8 million and hemoglobin 12 gm., 78 per cent. The urine was negative. The preoperative diagnosis was left ruptured ectopic tubal pregnancy. A dilatation and curettage revealed a moderate amount of tissue grossly identified as decidual tissue. A midline abdominal incision was made and a moderate amount of free and clotted blood was found in the cul-de-sac of Douglas. The left ovary showed a large recently ruptured corpus luteum which contained a firm clot and was not actively bleeding. The right ovary contained a normal appearing unruptured corpus luteum. A left salpingo-oophorectomy and appendectomy was done. The pathologist reported that the appendix measured  $9\frac{1}{2}$  by  $\frac{3}{4}$  cm., and appeared grossly normal. The ovary showed a large hemorrhagic corpus luteum with diffuse hemorrhage. Endometrial curettings showed chorionic villi. The tube and appendix were microscopically normal. The final diagnosis was: (1) incomplete abortion, (2) ruptured left corpus luteum with hemorrhage, (3) intact right corpus luteum.

CASE 2.—L. F., aged 25, single, office worker, was admitted to the hospital Aug. 5, 1937 with a diagnosis of possible acute appendicitis. She had always been in excellent health; however, twenty-four hours prior to admission, while riding in an

The temperature varied from subnormal to a maximum of 101.2° F. The pulse varied from normal to 130/minute. Pelvic examination was recorded 15 times, rectal examination three times, and in 17 instances there was no record of either pelvic or rectal examination. Of the 15 pelvic examinations recorded, six patients were reported to have had bilateral adnexal tenderness and no masses. Eight had right adnexal tenderness associated with an enlarged right ovary. One patient had an enlarged and tender left ovary. The three rectal examinations recorded and which were done on unmarried girls revealed right adnexal tenderness only.

Among the patients operated upon there were 25 nulliparas and 5 multiparas whose ages ranged from 14 to 32 years. Twenty-six of these women were between 14 and 22 and the remaining 6 between 22 and 32 years of age. Ruptured Graafian follicle with intra-abdominal hemorrhage occurred only once in the multiparous group.

Since there is normally a certain degree of regularity associated with follicle formation, ovulation, and corpus luteum appearance, one would expect to be able to correlate rupture of the Graafian follicle or corpus luteum and hemorrhage with the menstrual cycle. Table II gives this relationship.

TABLE II

MENSTRUAL DAY	RUPTURED GRAAFIAN FOLLICLE	RUPTURED CORPUS LUTEUM
1-14	14 Cases	None
14-21	2 Cases	1 Case
21-31	None	7 Cases
Intramenstruum	None	1 Case
Not stated	2 Cases	3 Cases

Of the 18 cases of Graafian follicle rupture with hemorrhage, 14 occurred between the twelfth and eighteenth days, one on the tenth day, and one on the twenty-first day. In the remaining three cases there was no record of the menstrual day on which rupture occurred. Nine of the 12 cases of corpus luteum rupture of which we have information concerning the menstrual day, occurred between the twenty-first and thirty-first days. This is in keeping with the previously reported cases found in the recent literature.<sup>2, 4-6</sup> One patient was menstruating when admitted; however, this case was complicated by an undiagnosed incomplete abortion. From our material one must assume that corpus luteum rupture occurs during the last week of the menstrual cycle, whereas Graafian follicle rupture occurs most often during the intermenstruum.

The degree of hemorrhage found at operation in the two conditions is outlined in Table III.

TABLE III

	SLIGHT, LESS THAN 30 C.C.	MODERATE, LESS THAN 100 C.C.	PROFUSE, LESS THAN 500 C.C.	NOT STATED
Graafian follicle	9 Cases	None	4 Cases	5 Cases
Corpus luteum	None	5 Cases	7 Cases	



coming on during coitus. The patient said she became weak, nauseated, and vomited once. These symptoms came on about ten minutes after the pain. Her last normal menstrual period was Feb. 26, 1936 and was uneventful.

The physical examination was negative except for tenderness in the right lower quadrant. Pelvic examination revealed normal internal genitalia except for the right adnexa which were very tender on palpation. They did not seem enlarged. Motion of the cervix caused right sided pain. The white blood count was 11,800 with 89 per cent neutrophils. The urine was negative, and the temperature and pulse rate were normal. The tentative diagnosis was ruptured right Graafian follicle with slight hemorrhage. The patient remained in the hospital for three days during which time she recovered completely. The white blood count on the third day returned to normal.

CASE 6.—J. L., aged 17 years, unmarried, had her last normal menstrual period on Sept. 16, 1936. While at work in the hospital on Sept. 29, 1936 as an undergraduate nurse, she was suddenly taken with a sharp right lower quadrant pain which caused her to double up. She stated that for the next half hour she became very weak and nervous. The pain was sharp at first, changed to a dull ache throughout the lower abdomen, and was worse when she walked. She had never experienced anything like this before.

Physical examination was essentially negative except for some deep palpable tenderness in the right lower quadrant below McBurney's point. Rectal examination revealed pain on motion of the cervix and a tender right adnexa which did not appear enlarged. The left adnexa were neither tender nor enlarged. The white blood count was 12,800 with 84 per cent neutrophils. The urine was negative, and the temperature was 99° F. The dull pain continued until 7:00 A.M., September 30, after which time it gradually subsided. The white blood count September 30 was 8,000 with 70 per cent neutrophils. October 1, the white blood count was 6,200 with 62 per cent neutrophils. The patient was discharged with a presumptive diagnosis of ruptured right Graafian follicle with slight hemorrhage.

#### SUMMARY AND CONCLUSION

1. Thirty cases of Graafian follicle and corpus luteum rupture with hemorrhage, operated upon with a tentative diagnosis of appendicitis or ruptured ectopic pregnancy, are reported.

2. Five additional cases are discussed. These patients were observed in the hospital for a maximum period of five days, and a clinical diagnosis of ruptured Graafian follicle with slight bleeding was made. All recovered without the aid of surgery.

3. The differential diagnosis between rupture of Graafian follicle and corpus luteum with hemorrhage and appendicitis or ectopic pregnancy is discussed.

4. The only characteristic symptom noted in rupture of Graafian follicle and corpus luteum was sudden pain and this occurred in every instance.

5. In this series rupture of the ovarian sexual apparatus occurred most frequently in young women up to 25 years of age and most often on the right side.

6. Correlation between ruptured Graafian follicle and corpus luteum with bleeding and the menstrual cycle is mentioned.

7. Similar quantities of blood loss were noted in both Graafian follicle and corpus luteum rupture.

8. It is suggested that when the diagnosis of lower abdominal conditions warranting surgery in the female is in doubt either right rectus

auto, she was suddenly taken with sharp knifelike pains in right lower quadrant. She went directly home and obtained partial relief by lying in bed. She experienced some nausea but no vomiting. There had been no constipation. The pain which was in the right lower quadrant changed to a dull ache, spreading over the entire lower abdomen and was made worse on motion. The next day the patient went to work but she did not feel right. She was advised to enter the hospital. The last normal menstrual period occurred July 22, 1937 and was uneventful.

Physical examination was negative except for tenderness in the right lower quadrant below McBurney's point. There was slight right rectus spasm. Pelvic examination was negative except for a tender right ovary. On August 6, the white blood count was 9,000 with 57 per cent neutrophiles and the urine was negative. On August 7, the white blood count was 9,800 with 74 per cent neutrophiles. On August 8, the white blood count was 6,200 with 70 per cent neutrophiles. The patient remained in the hospital under observation for three days during which time she recovered completely and was discharged with a diagnosis of ruptured right Graafian follicle with slight hemorrhage.

CASE 3.—E. R., a single girl, aged 19 years, was admitted as an emergency case Jan. 22, 1936, because of right lower quadrant pain which came on suddenly about twenty-four hours previously. The patient stated that the pain was sudden and knife-like, causing her to sit down. Later she became weak but did not faint. Gradually the pain became dull and spread over the entire abdomen. She had vomited four times in the past twenty-four hours. The last normal menstrual period occurred Jan. 12, 1936.

Physical examination was negative except for direct and rebound tenderness over the lower abdomen, slightly worse over the right side. All the abdominal tenderness seemed centered in the pelvis. Pelvic examination was negative except for right adnexal tenderness. The right ovary seemed larger than normal. The white blood count was 15,300 with 77 per cent neutrophiles. The urine was negative. The patient was given an enema which did not relieve her condition. The diagnosis on admission lay between possible acute appendicitis, possible acute salpingitis and possible ruptured right Graafian follicle with mild hemorrhage. The patient remained in the hospital five days during which time she gradually (third day) recovered, with a gradual recession of the leucocyte count from 13,200 on January 23 down to 6,000 on January 26. The final diagnosis was ruptured right Graafian follicle with mild hemorrhage.

CASE 4.—M. L., aged 15 years, while in the process of getting out of bed Jan. 15, 1937 was taken suddenly with right lower quadrant pain which made her cry out and double up. She became weak and nauseated but did not vomit. The pain gradually became dull, and spread over the lower abdomen. Since the patient had been previously told she had a bad appendix she was immediately taken to the hospital. On admission she stated that she had had in the past year several similar attacks of lower abdominal pain but never so severe. Her last normal menstrual period was Dec. 30, 1936 and was uneventful. There had been no constipation.

The physical examination was negative except for some muscle spasm over both right and left lower quadrants. There was direct and rebound tenderness in the right lower quadrant below McBurney's point. No masses were palpated. Rectal examination revealed pain referred to the right side on motion of the cervix. The right adnexa were larger than the left and definitely tender. The white blood count was 10,000 with 68 per cent neutrophiles. Temperature was 99.2° F. and the pulse was 90. The patient remained in the hospital for three days during which time the symptoms completely disappeared. The white blood count was 6,000 with 52 per cent neutrophiles on the day of discharge. The final diagnosis was ruptured right Graafian follicle with slight hemorrhage.

CASE 5.—L. Mc., aged 22 years, a nullipara, entered the hospital as an emergency on March 7, 1936 because of a history of sudden knife-like lower abdominal pain

Among the procedures mentioned by Nürnberger, the cornual wedge operation is comparatively the most reliable and still used a great deal. No pregnancy has occurred among the 64 cases of my own material (Table I), which has been followed up for more than two years.

TABLE I. SIXTY-FOUR STERILIZATIONS BY CORNUAL RESECTION

INDICATION	NUMBER OF CASES
Operations for prolapse (41 vesicovaginal interpositions)	43
Tuberculosis of lungs	12
Organic heart disease	4
Tracheostenosis	1
Voluntary sterilization	1
During cesarean operation	3
Total	64

Although the result is satisfactory concerning sterilization, these statistics are somewhat misleading, as many of the patients sterilized in the course of an operation for prolapse were of an age when conception, though possible, was less likely to occur.

Furthermore, the table does not indicate the frequent difficulty of controlling hemorrhage, especially in pregnancy, after the excision of a sufficiently deep cornual wedge.

The complete elimination of hemorrhage is one of the reasons for the increasing popularity of the "bloodless" tubal ligature advised by Madlener, which I have used as the procedure of choice since it has been published.

It is the purpose of this paper to give an account of the merits of the tubal sterilization devised by Madlener, because I feel that of all the procedures employed, this one is the most satisfactory.

The original technique consists of lifting up a generous loop of the Fallopian tube and crushing it with a clamp. The clamp is removed, and replaced by a ligature of nonabsorbable material.

In Table II, 147 sterilizations in my own experience are recorded. Most of them have been performed while I was connected with the Department of Gynecology at the State University of Iowa in Iowa City.\*

In contradistinction to the cases of cornual wedge operation (Table I) these 147 sterilizations by the original Madlener method include only 58 patients with prolapse. The large majority were women of childbearing age, and in them the result was entirely favorable. The only failure occurred in a patient operated upon for prolapse.

Table III is a survey of all the cases reported in the literature up to September, 1938, as sterilized according to Madlener, including the author's 147 cases and the 157 sterilizations performed at the Gynecological Clinic of the Iowa University Hospital since July, 1934.

\*I am indebted to Dr. E. D. Plass who has allowed me to present this material as well as the number of patients operated upon at the Department of Gynecology from July, 1934 to September, 1937, listed in Table III.

or midline incisions should be made, so that visual inspection of the internal genitalia may be accomplished.

9. Abstracts of five unoperated cases diagnosed ruptured Graafian follicle with slight intra-abdominal hemorrhage but not proved are presented. A case of ruptured left corpus luteum with hemorrhage complicated by incomplete intrauterine abortion is reported.

I wish to express my appreciation to Dr. Charles C. Pinkerton for many valuable suggestions in the preparation of this report and also to thank the Surgical Staff of the City Hospital of Akron for their permission to publish the cases herein reported.

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## TUBAL STERILIZATION BY THE MADLENER TECHNIQUE\*

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**D**URING recent years, the importance of contraception as well as sterilization for medical eugenic and social reasons in selected cases has gained widespread recognition.

Side by side with the endeavor of the numerous birth control clinics to find a reliable method of contraception, increasing attention has been given to the question of dependable permanent sterilization of women.

In men, sterilization is no longer a problem. Vasectomy is unanimously accepted as the procedure of choice because it fulfills, when properly performed, the requirements of ideal sterilization, including (1) absolute reliability, (2) minimum operative risk, (3) subsequently unimpaired health, and (4) undisturbed sex response.

In women, sterilization is still open to discussion. Female fertility has an amazing persistence. On one hand we may see it destroyed by an apparently insignificant infection. On the other hand we find it surmounting heavy odds. Conception has taken place after the removal of both tubes as in the cases reported by Lasch, Burkhard, Zangemeister, and once even following subtotal hysterectomy in a case reported by Liepman.

Considering this ability of the female organs to fulfill their biologic purpose, it is no wonder that surgical sterilization has met with difficulties. Nürnberger recorded in a comprehensive study of 305 sterilizations by various methods, 17, or 6 (5.7) per cent, failures.

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the pregnancy was located in the Fallopian tube of the three cases mentioned by Goldschmidt, Heimann, and Hüsey. Even with the addition of these six failures, there is only one failure in over 200 sterilizations by this method.

Before discussing the failures in relation to surgical technique, I want to point out, as a possible source of disappointment, that the patient may be pregnant at the time of operation. I have seen a woman who denied having had intercourse because she thought the operation would do away with a possible pregnancy. Actually, she had conceived nine days before operation.

It is likely that other of the reported failures had the same origin. Therefore it is advisable to do a curettage if there is any doubt of the reliability of the patient's statements. Operation even immediately following menses does not exclude the possibility of an early pregnancy.

Another source of failure which has nothing to do with the actual technique of the ligature is the confusion of the Fallopian tube with the round ligament. Köhler first warned against this error and Schultze has reported a case in which the ligature was actually placed on the round ligament by mistake.

In the vaginal performance of the Madlener procedure, I well understand how this may happen and there is every reason to believe that the single failure among my own cases was due to this error. Especially in teaching, it is necessary to emphasize this pitfall.

Failures due to technique fall into two principal categories: (1) The ligature, becoming loose, does not stay in the crushed furrow or the entire loop of tube slips out. This has been demonstrated by Fraenkel in his animal experiments, the salpingographic studies of Fuchs-Lark, Wolf, and Thiessen, and the relaparotomies of Koller and Otto; (2) The histologic examination of specimens (Rubowits-Kobak, Adair) has shown that the proliferating epithelium of the tubal mucosa may establish ducts or fistulas which circumvent the ligated area. In addition, communication may be re-established by its tunnelling through the scar tissue and opening a new tubal canal. I feel that the formation of fistulas is encouraged by laceration of the serous covering of the tube.

These mishaps may be avoided by taking a generous loop and by exercising care in the application of the crushing instrument. The security of the ligature is greatly increased by using nonabsorbable material and by carrying the suture through the mesosalpinx and tying it separately around each leg of the loop (Markowsky).

It is because of the possibility of the ligature's slipping that I do not favor cutting the tube as Pomeroy and others have advised. If the tubal loop is cut, careful peritonization is required. This complicates the procedure without giving additional advantages over the original Madlener.

With the observance of these simple precautions, the Madlener method should prove the most reliable means of permanent sterilization. Its simplicity and the absence of bleeding qualify it for vaginal performance.

TABLE II. 147 STERILIZATIONS BY ORIGINAL MADLENER TECHNIQUE (PERSONAL CASES)

INDICATION		NUMBER OF CASES	
Operations for prolapse (38 vesicovaginal interpositions)		58	(1 failure)
Pulmonary tuberculosis (1 bronchiectasis, 1 lung abscess)		15	
Organic heart disease		12	
Pelvic pathology		5	
Spondylitis		1	
Kidney disease		6	
Eye diseases		3	
	Feeble minded	10	
	Dem. precox	1	
	Psychosis	8	
Mental and organic brain diseases	Mult. sclerosis	2	27
	Encephalitis	1	
	Epilepsy	5	
Social		17	
Voluntary		3	
Total		147	

TABLE III. TUBAL STERILIZATIONS (MADLENER PROCEDURE)

OPERATOR	YEAR OF PUBLICATION	NUMBER OF CASES	FAILURES
Madlener	1919 and 1932	166	0
Weber (Munich)	1923	50	0
Schreiner, R.	1927	84	0
Bakscht (Russia)	1929	29	0
Eyding, A.	1933	63	0
Macke (Düsseldorf)	1933	21	0
Rubowits and Kobak	1934	75	4
Otto	1934	117	0
Sänger	1934	620	0
Koller, Waser, Frey Walther (Zurich)	1934	1,500	8
Köhler (Hamburg)	1934	250	0
Holtermann (Cologne)	1935	250	0
Runge (Heidelberg)	1936	600	0
v. Graff	1936	147	1
Iowa Gyn. Clinic since July, 1934	1937	157	0
15 Reporters		4,279	13 = 0.3%
Additional failures reported			6
			19 = 0.44%

The Madlener technique has been successful in 99.6 per cent.

There is somewhat less than 100 per cent success. It is to be expected that the 0.3 per cent failures can be reduced further if not entirely eliminated by technical proficiency.

Although it may be assumed that the cases reported in the literature have been properly followed up, exact data as to the time elapsed since the operation have not been recorded. The 147 cases of my own experience have been followed up for four and more years, and the additional 157 cases of the Iowa Clinic, from two to four years.

In Table III, I have conscientiously included six failures reported in the literature without their counterbalance of successful cases. Adair has seen two cases; Döderlein, one, of uterine pregnancy following Madlener sterilization in the course of a cesarean section, while

4. The causes of failure are pregnancy at time of operation, mistaking the round ligament for the Fallopian tube, slipping of the ligature, and lacerations of the serosa which encourage fistula.

5. The cutting of the tied loop of the tube is likely to invite failures and therefore should be omitted.

6. The advantages of the vaginal route in the performance of sterilization as well as pelvic surgery in women on the whole are emphasized.

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728 PARK AVENUE

## TYPHOID FEVER IN PREGNANCY\*

### PROBABLE INTRAUTERINE TRANSMISSION OF THE DISEASE

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TYPHOID fever is rare among pregnant women; only two such patients have been observed among more than 11,000 obstetric admissions to the University Hospitals between Jan. 1, 1926, and March 1, 1939. The case here reported is unique in that a woman convalescent from typhoid fever gave birth to a child presenting presumptive evidence of the intrauterine transmission of the disease. The presence of a positive agglutination reaction for typhoid in the blood and the recovery of the typhoid bacillus from the feces of the newborn child appears to warrant this presumption. This case report is of further interest because of the high content of H and O typhoid agglutinins in the breast milk and because of the carrier state of both mother and baby.

\*Assistance on the bacteriologic aspects of the problem was furnished by Dr. I. H. Borts.

In using the vaginal route, the Fallopian tubes can be approached in either of two ways: (1) anteriorly, after dissection of the bladder through the vesicovaginal fold, (2) posteriorly, through Douglas' pouch. A number of authors prefer the Douglas pouch route as routine procedure in vaginal hysterectomy. Burch recommends it in particular for tubal sterilization in order to circumvent possible difficulties in the dissection of the bladder.

Personally, my preference is for the incision of the vesicovaginal fold because of the ideal fixation of the uterus which can be obtained by placing a clamp on the round ligament. My preference for the vaginal approach is evidenced by the fact that I have used it among the 211 sterilizations of my own material, i.e., 64 by tubal wedge operation and 147 according to Madlener, but in 4 cases of sterilization in the course of cesarean operations.

Vaginal operation has numerous advantages. Primarily, it is in the best interests to the patient because it minimizes surgical risk, the dread of operation and the period of incapacity. The anesthesia is brief and the operative shock eliminated. Postoperative discomfort is negligible and the patient is usually up on the third day. In five to seven days, she is able to leave the hospital and resume her ordinary activities.

Involving no abdominal incision or resultant scar, the vaginal operation carries no suggestion of mutilation. This is of vital importance in reducing the psychic effects of sterilization. With the element of complete security, it is likely to improve the sex relationship and favor response. The patient's subsequent health is unimpaired and her psychic adjustment very likely to be improved. Considering the average income of our public, the saving of hospital days should be an important factor. Since the majority of sterilizations are among the needy and in those in public institutions, their performance by the vaginal route assumes great economic proportions.

The advantages of the vaginal performance of the Madlener hold equally true for a great number of gynecologic operations. By conservative estimate one-third of all pelvic surgery routinely performed by laparotomy can be efficiently accomplished by the vaginal route, with an average reduction of the hospitalization time of 50 per cent. This would not only mean a considerable economy of the entire costs of such operative gynecologic cases, but actually increase the capacity of the department. Therefore, both for medical and social reasons, the instruction in vaginal technique should be given more attention in our medical schools.

#### SUMMARY AND CONCLUSIONS

1. The tubal sterilization according to Madlener is recommended as the procedure of choice in the permanent sterilization of women.
2. The advantages of the original Madlener over other methods including the cornual wedge operation, are described.
3. 4,279 cases from the literature have proved successful in 99.7 per cent. This includes 304 cases reported for the first time by the author, with only one failure.



reaction from vaccination for smallpox. Again on the fifty-first to fifty-fifth days of life the temperature ranged between 101° and 104° F. Nothing was found on physical examination to explain this rise. The baby was discharged from the hospital at the age of 64 days.

*Follow-up.*—Subsequently, information was obtained that the baby on the seventy-fourth day of life had a sudden rise in temperature to 104° F. with signs of colic, which persisted for a few days. At the age of ninety-two days it was apparently well, having approximately doubled its birth weight.

TABLE I. BACTERIOLOGIC STUDIES ON W. H.

DATE	FECES	URINE	BLOOD	BILE BREAST MILK	BLOOD AGGLUTINA- TIONS	MILK AGGLUTINA- TIONS	REMARKS
9/13/38			+		1/1280		Nine cultures made from the feces and two from the urine during this in- terval
9/15/38	+	+	+		1/1280		
9/16/38	+	+	+				
9/17/38	+	+					
to 10/27/38							
10/31/38	+	-		+	1/1280		Culture from cer- vix + for <i>B. typhosus</i>
11/ 4/38							
12/20/38	+						
12/29/38	Spontaneous delivery						
1/ 2/39				-		1/1280 (whole milk)	
1/ 6/39							
1/ 7/39		-	-		O = 1/2560 H = 1/640		
1/ 9/39						O = 1/5120 H = 1/2560 (whey)	
2/ 1/39	Cholecystectomy: The mucosa of the gall bladder was (+) for <i>B. typhosus</i> while the appendix was (-)						
2/ 2/39	+				O = 1/320 H = 1/640		Four cultures made from the feces and one from the urine
2/ 7/39							
2/ 8/39	+	-					
2/15/39	-						
2/20/39	+						
2/21/39	-	-					
to 2/27/39							
3/ 2/39	-				O = 1/320 H = 1/1280		

*Pathology.*—The gross specimen consisted of a gall bladder which had been opened and fixed in formalin. When spread out, it measured 8 by 6 cm. The serosal surface was somewhat ragged, but in the center there was a smooth strip of peritoneum, which was free from adhesions. The wall was slightly thickened. There was no evidence of acute inflammation. The mucosa was intact. Ten small brown stones accompanied the specimen.

Microscopically the wall of the gall bladder was slightly thickened and infiltrated by chronic inflammatory cells. The epithelial lining was intact.

Histologically the appendix showed mild chronic inflammatory changes in the wall of a nonspecific type.

*Diagnosis:* (1) "Chronic cholecystitis and cholelithiasis." (2) "Mild chronic appendicitis."

## CASE REPORT

W. H. (No. 38-27918), a 21-year-old married white gravida ii, was admitted to the University Hospitals on Sept. 14, 1938.

This patient had been delivered spontaneously of a 2,400 gm. baby in this hospital in February, 1937. During the subsequent eighteen months there were several attacks of colic in the right upper abdominal quadrant. These pains radiated to the right shoulder blade. There was concomitant nausea and vomiting but no history of jaundice.

The menstrual history was normal. The last menstrual period began March 5, 1938, and the expected date of delivery was Dec. 12, 1938.

The onset of the present illness, two weeks before admission (thirty weeks after the last menses) was characterized by general malaise, low backache, sore throat, nausea, vomiting, chills, and persistent fever. There was no history of rose spots, diarrhea, tympanites, or epistaxis.

On admission the temperature was 103.8° F., the pulse rate was 140, and the respirations were rapid (40 per minute) and shallow. The patient was acutely ill, dehydrated, drowsy, and the speech, although coherent, was slow and thick. The pupils reacted to light, the thyroid was not palpable, and the lungs were clear to percussion and auscultation. The heart was not enlarged, and the rhythm was regular, but a faint systolic murmur was heard at the apex. The blood pressure was 110 systolic and 74 diastolic. The lower pole of the spleen was barely palpable. All the deep reflexes were present but diminished. There was no peripheral edema. The uterus, extending slightly above the umbilicus, was estimated to be the size of a six to seven lunar month pregnancy. Fetal heart sounds were not audible. The vaginal outlet was marital, well supported, and free of discharge. The cervix was soft and closed, and the vaginal mucosa was bluish in color.

*Laboratory Findings.*—The urine was normal, except for a moderate albuminuria. The red blood cell count was 2,700,000 and the hemoglobin was 10 gm. per cent (Haden-Hauser). The red cells showed some variation in size, shape, and staining qualities. The total leucocyte count was 10,000. A differential count revealed 66 per cent lymphocytes, 3 per cent monocytes, 28 per cent polymorphonuclear leucocytes, and 3 per cent unclassified leucocytes. The blood Wassermann and Kline reactions were negative. The blood showed positive agglutinins for *B. typhosus* in a dilution of 1/1280. Cultures from the urine, feces, and blood stream were positive while those from the colostrum were negative for typhoid.

*Course in the Hospital.*—The course of the patient was rather stormy for the first week after admission, but the temperature gradually reached normal on September 30 and thereafter was not elevated.

From September 26 to 30, there was a transient bilateral mastitis which was treated conservatively. Albumin was not present in the urine after October 2. The bile, which was obtained through a duodenal tube, and the stools continued to show typhoid organisms (see Table I). On December 29, following a seven-hour labor, the patient was delivered spontaneously from L.O.A. position of a living, male infant, weighing 2,745 gm. The puerperium was afebrile. On Jan. 2, 1939, the breast milk agglutinated typhoid bacilli in a dilution of 1/1280. Five days later, the centrifuged whey produced agglutination in dilutions of 1/5120 and 1/2560 for the O and H antigens, respectively. A cholecystogram (oral dye) on Jan. 13, 1939, revealed a poorly functioning gall bladder containing several stones. Following cholecystectomy on Feb. 2, 1939, typhoid bacilli were demonstrated by culture in the mucosa of the gall bladder. The stools obtained after February 20 did not contain the organism.

The mother handled the infant once shortly after birth for approximately twenty minutes. The child's course was not unusual except that *B. typhosus* has been cultured repeatedly from the stools. The blood serum agglutinated the H antigen at a dilution of 1/640 on the second and ninth days, at 1/160 on the thirty-ninth, and at 1/80 on the sixty-third day of life. The agglutination test for the O antigen and attempts to grow *B. typhosus* from blood clot cultures on three different occasions gave negative results. From the twenty-fifth to thirty-first day of life the baby had a fever of 100° to 102° F. and a rash simulating miliaria rubra. It was believed, however, that the temperature elevation was due to a moderately severe

(father) localization had occurred in the gastrointestinal tract but was proved not to be in the biliary system, and in the third (baby) the location was not established. The condition noted in the mother confirms the observations of Boyd<sup>15</sup> and Borts<sup>16</sup> that over 95 per cent of typhoid carriers have chronic cholecystitis often associated with stones. The carrier state, in the infant presented, may be due either to localization of the bacilli in some part of the intestinal tract or in the biliary system. If it is assumed that Bolton's hypothesis is correct, the latter site seems the most probable.

All other authors have found the agglutinin content in the breast milk to be low. By using the method described by Hall and Learmonth,<sup>17</sup> who observed that the fat in milk interferes with the agglutination reaction, and, therefore, made tests on the whey, our results showed much larger quantities of both O and H agglutinins in the milk than in the blood. Newman<sup>18</sup> has noted similar reactions in cows with undulant fever. He was of the opinion that the protein fraction of the blood serum, which carried these immune bodies, became concentrated and stored in the colostrum. It was also demonstrated that if newborn animals were given colostrum rich in antibodies, the recipient's blood serum will in a few hours show a positive reaction against malta fever. Such was the experience of Talamon and Castaigne<sup>19</sup> who reported a woman developing typhoid fever four months post partum. The baby was allowed to nurse from the breast for the first month of the disease. It was then weaned for a few weeks. Subsequently breast feedings were resumed. They noticed that as long as the baby took breast milk the blood showed a positive Widal reaction, but a few days after discontinuing the breast milk the Widal reaction became negative.

On the night following birth, the baby, here described, was taken to breast by mistake. It is possible that the positive Widal reaction of the baby's serum reported shortly after nursing could have been due to absorption of agglutinins from the colostrum. However, it is the opinion of the authors that this exposure had very little to do with the persistently positive reaction of the serum and that the infant produced its own agglutinins.

Although the baby went to breast only once, in this particular case, there did not seem to be any contraindication to breast feeding. If the mother were a carrier and the baby had no evidence of infection, weaning would seem to be desirable.

#### SUMMARY

A case of probable intrauterine typhoid fever in a baby born of a mother convalescent from typhoid is described. The principal observations of significance were: the high agglutinin content of the breast milk against typhoid fever; the presence of typhoid bacilli in the baby's stools; and the carrier state of the mother and baby. Typhoid organisms were found in the maternal bile obtained by duodenal drainage. Cholecystectomy was performed during the fifth post-partum week. The gall bladder contained stones and typhoid bacilli were cultured from the mucosa. In all probability, the infant formed its own agglutinins.

*Epidemiology.*—The State Epidemiologist reported that the patient lived in a small village and that the family obtained milk from their own cow. They used an outdoor toilet and shared the use of a well with another family. The well, covered with planks, was not situated in a depressed or low area. The patient ate food identical with that eaten by other members of the family: the husband, a son, and a brother. The husband was admitted to the University Hospitals on Oct. 3, 1938, treated for typhoid fever, and later discharged as a typhoid carrier. The brother was sick for a period of six weeks in October and November. It was reported that he had influenza, but it is probable that he may have had typhoid fever. The son is not known to have been infected.

#### LITERATURE

Lynch<sup>1</sup> reported a typhoid fever incidence of 2.8 per cent among pregnant women admitted to the Johns Hopkins Hospital, and Freund<sup>2</sup> recorded an incidence of 1.28 per cent from 10 of the larger European cities.

Pregnancy evidently does not alter the prognosis of the disease. Hicks and French,<sup>3</sup> in 1905, reported a maternal death rate of 14 to 17 per cent but emphasized the fact that the effect of the disease on pregnancy is bad, as abortion or premature labor occurred in the majority of cases. Morse<sup>4</sup> summarized the factors which have been advanced to explain spontaneous premature interruption of the pregnancy and considered the most important to be: (1) the absorption of toxins by the fetus, and (2) intra-uterine typhoid fever resulting in fetal death.

Seventy-eight case reports of typhoid fever occurring during pregnancy were collected from the literature (Lynch;<sup>1</sup> Hicks and French;<sup>3</sup> Morse;<sup>4</sup> Griffith and Ostheimer;<sup>5</sup> Ratliff;<sup>6</sup> Rosensohn;<sup>7</sup> Ferri;<sup>8</sup> Laffont and Mèle;<sup>9</sup> Wing and Troppoli;<sup>10</sup> Patoir and Gelle,<sup>11</sup> and Sai<sup>12</sup>). In 18 cases the details were incomplete and the diagnosis may well have been erroneous, since they occurred before the Widal agglutination test was perfected. Among the remaining 60 satisfactory cases, 29 developed the disease before the period of fetal viability. Five of these women eventually went to term and were delivered of living mature babies. The other 31 women, in whom the disease appeared during the last trimester of pregnancy, were also delivered of living infants but only 17 of their babies survived longer than four days. In one case *B. typhosus* was demonstrated in the lochia.

Klein<sup>13</sup> in 1911 presented evidence that in the majority of cases the immunity in the baby was passive; agglutinins pass through the placenta from the mother to the infant. In all of those cases collected from the literature, the serum reaction was negative and typhoid bacilli could not be isolated from the spleen, bone marrow, liver, etc., at autopsy in the fetuses where the intrauterine exposure to the disease had been less than three weeks. Presumably, the placenta acts as a temporary barrier. Morse was of the opinion that the infant was not affected until damage had occurred to the placenta. Bolton<sup>14</sup> described the different pathologic changes appearing in infants before and after birth. Those infected in utero had no demonstrable lesions in the gastrointestinal tract, whereas in postnatal infections such lesions were prominent, as in adults. He was of the opinion that neonatal infections were due to mouth contamination while prenatal infections were probably by way of the blood stream.

The Widal reaction, which was recorded in 38 out of 79 infants, was positive in 17 (included a set of twins) and negative in 21. In the other 41 cases the reaction was not reported. In one of those having a positive Widal reaction, typhoid bacilli were noted in the wall of the umbilical cord, and in another the typhoid organisms were isolated for the first time from the stools. The authors, who reported the latter case, were of the opinion that the baby formed its own agglutinins.

#### COMMENT

Approximately 2 per cent of all individuals having typhoid fever remain carriers, the causative organism usually persisting in the biliary system or the intestine. In the family here recorded three carriers were found. In one (mother) the organism was in the gall bladder, in another

In their dehydration experiments Maddock and Collier<sup>2</sup> found that normal individuals will retain urine solids if the urine volume is below 500 c.c. in twenty-four hours.

Gamble<sup>3</sup> described the changes in electrolyte due to abnormal losses of body fluid. When vomiting is present several factors must be considered. The body loses water and electrolyte and may suffer from starvation. If the water loss is great there is not sufficient urine water to excrete all urine solids presented to the kidneys. As gastric juice is composed chiefly of HCl, persistent vomiting causes a serious loss of chlorides. Chloride ions are lost in excess of sodium ions. The structure of the blood plasma and interstitial fluid is almost identical, each containing sodium as the chief cation and chloride and bicarbonate as the chief anions. With a loss of chlorides, as in vomiting, there is a compensatory mechanism which increases the bicarbonate proportion. This tends to produce a state of alkalosis, or if the pH is normal, a compensated alkali excess will occur if chlorides are lost and if the individual is able to maintain a water intake sufficient to permit the kidneys to excrete all of the urine solids presented to them. Because no renal impairment exists there will be no increase in blood urea or nonprotein nitrogen. The carbon dioxide combining power will be increased.

If the fluid intake is too small to permit the kidneys to excrete all urine solids, some will be retained. This produces a further change in the electrolyte structure of the extracellular fluid. Some of the space formerly occupied by chlorides will be replaced by the retained urine solids as phosphates, sulphates, and inorganic acids. The increase in bicarbonate will be less than in the individual excreting all urine solids.

In the presence of starvation ketone acids form. As they are carried in the same compartment as chlorides and bicarbonate, some bicarbonate will be displaced. A positive acetone test in this instance indicates a ketosis, not an acidosis.

#### HYPEREMESIS GRAVIDARUM

Peckham<sup>4</sup> reported the laboratory findings in 60 cases of hyperemesis gravidarum. His findings agreed with those of Dieckmann and Crossen<sup>5</sup> and others. The records studied were grouped as mild and severe. In the mild cases there was no great change in the blood nonprotein nitrogen, or uric acid. Chlorides were reduced. There was an increase in the carbon dioxide combining power in some, in others a decrease. In the severe cases there was a marked increase in the blood nonprotein nitrogen and uric acid, the chlorides were greatly decreased and the carbon dioxide combining power varied from a marked increase to a marked decrease.

As chlorides are lost clinical symptoms quite similar to those noted in hyperemesis gravidarum develop. The most prominent are weakness, vomiting, drowsiness and finally even twitching and coma. It is, therefore, logical to assume that, as plasma chlorides are always decreased when vomiting of pregnancy is severe, the condition could be improved by the addition of chlorides. If renal function has been impaired by dehydration, fluids must be forced. A logical treatment for hyperemesis gravidarum is as follows: (1) Improve renal excretion, (2) restore a normal electrolyte structure, (3) remove abnormal ketone acids, and (4) maintain a normal fluid and acid-base balance.

*Improve Renal Excretion.*—In extensive dehydration renal function is impaired as a result of marked concentration of urine solids. Isotonic

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## WATER EXCHANGE AND SALT BALANCE IN HYPEREMESIS GRAVIDARUM

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WHATEVER the basic cause, vomiting occurs in a large proportion of pregnant women. Persistent vomiting, with extensive loss of water and chlorides, leads primarily to dehydration and alteration in the electrolyte pattern of the extracellular fluid and secondarily to starvation. Approximately 70 per cent of the body weight is made up of water. Fifty per cent is intracellular and 20 per cent extracellular. The extracellular water is divided into interstitial water and blood plasma. The interstitial water, including lymph, represents 15 per cent of the body weight. The vascular fluid accounts for approximately 5 per cent of the body weight. Body water holds electrolyte in solution, and changes following loss of electrolyte may be serious.

Lashmet and Newburgh<sup>1</sup> found that normal individuals need approximately 500 c.c. of urine water to permit the kidneys to excrete all urine solids. If the urine volume falls below this amount in normal individuals, retention of urine solids will result. In renal disease they found that as the concentrating ability was lowered more urine water was necessary to remove all urine solids. They calculated the loss of water through the skin and lungs. This was called water of vaporization. Vapor water is always expended even though there is a shortage of urine water. To be reasonably certain that the kidneys are permitted sufficient water to excrete all urine solids presented to them, Newburgh<sup>1</sup> and Maddock and Collier<sup>2</sup> found that the individual should have the following needs supplied:

Vapor water	1,000 c.c.
Urine water	1,500 c.c.
Stool	200 c.c.
<hr/>	
Total	2,700 c.c.
Plus any abnormal loss.	

will furnish an adequate amount of salt if the plasma chlorides have reached normal limits, providing there are no abnormal losses. If vomiting persists, the emesis should be measured and an equal amount of normal saline added to the basal requirement for that twenty-four-hour period. Isotonic dextrose is then given in amounts sufficiently large to furnish a daily urine output of between 2000 and 3000 c.c. Isotonic dextrose will supply a low caloric intake and in addition maintain an adequate renal excretion.

As the signs and symptoms resulting from hypochloremia disappear, the patient will usually retain small frequent feedings. Soluble phenobarbital in small amounts subcutaneously, or phenobarbital by mouth will provide adequate sedation.

#### MILD VOMITING OF PREGNANCY

Mild vomiting occurs in about 50 per cent of all pregnant women. To prevent hyperemesis gravidarum these patients must be treated. The only serious early defect produced by vomiting is a loss of body chlorides. Most patients can replace chlorides if properly instructed. The ordinary 00 gelatin capsule will hold 1.0 gm. of NaCl. This amount of salt taken with approximately two-thirds of a glass of water will furnish volume for volume replacement of chlorides lost by vomiting. Salt is retained readily when taken in capsule form. Salt must be accompanied by water to permit the body to retain it. In addition to salt replacement, enough water must be ingested to maintain an adequate urine output. Most patients can drink sufficient fluid to enable them to excrete three pints of urine in each twenty-four hours. It has been possible following this regime to prevent persistent vomiting if treatment is started early. The patients are instructed to eat small, low fat meals frequently. Mild sedation is obtained by giving phenobarbital two or three times daily in half grain doses.

#### COMMENT

The reported blood chemistry findings in hyperemesis gravidarum indicate that the mild cases have a slight reduction in plasma chlorides, with little evidence of nitrogenous retention. Patients with persistent vomiting reveal a marked reduction in plasma chlorides, and give evidence of nitrogenous retention. Glassman<sup>7</sup> reported an average plasma chloride value in hyperemesis gravidarum of 489 mg. per cent and considered this reading essentially normal. Peters and Van Slyke<sup>8</sup> and Bartlett, Bingham and Pedersen<sup>9</sup> report normal plasma chloride values to be between 560 and 630 mg. per cent. Bartlett and others emphasize that when plasma chloride values are as high as 500 mg. per cent, symptoms of hypochloremia will be present in some patients. They warn that any loss of electrolyte and water is important and must be replaced if the chemical processes of the body are to be efficient.

The cause of hyperemesis gravidarum is not known, but it is known that there is a reduction in plasma chlorides with an alteration in electrolyte structure. As vomiting persists, dehydration develops, urine volume decreases, renal impairment occurs, and retention of urine solids takes place. Teitelbaum<sup>10</sup> has found that there is no direct relationship

dextrose solution, rapidly oxidized when given intravenously, provides an excess of water which makes it possible for the kidneys to excrete urine in a normal fashion. As urine solids will have been retained for some time in persistent vomiting, a large amount of urine water is desirable. In addition to the requirements for replacement of electrolyte, sufficient isotonic dextrose should be given to insure a twenty-four-hour urine output of 3,000 c.c. This large urine output will restore adequate renal efficiency and as a result the kidneys may regulate the excretion of excess substances in the body fluid. By giving isotonic dextrose in sufficiently large quantities, renal impairment will be overcome and retained urine solids will be excreted. This is an important step in the restoration of a normal electrolyte structure.

*Restoration of Normal Electrolyte Structure.*—There is a considerable shortage of chlorides when vomiting has persisted for some time. Collier<sup>6</sup> and associates found the low level of normal plasma chlorides to be about 560 mg. per 100 c.c. Collier states that death may occur when the plasma chlorides fall to approximately half the normal level. Mild symptoms are present when the plasma chlorides drop to 500 mg. per 100 c.c. and serious symptoms when they are around 400 mg. per cent. Normal saline contains 8.5 gm. of salt in each 1000 c.c. of water. When equal amounts of sodium and chloride are given, the kidneys must excrete excess sodium in order to allow the body fluid to retain needed chlorides. It is important to restore the excretory power of the kidneys if the electrolyte structure is to be repaired by the addition of sodium chloride.

The amount of sodium chloride necessary to restore normal plasma chlorides must be determined. If the replacement is inadequate, vomiting will persist and there will be a continued loss of chlorides. Collier<sup>6</sup> and associates have developed an ingenious formula for determining the amount of salt necessary to raise the plasma chlorides to a normal level. They found that for each 100 mg. per 100 c.c. that the plasma chlorides were to be raised, 0.5 gm. of sodium chloride should be ingested for each kilogram of body weight or 0.2 gm. of sodium chloride for each pound of body weight. Using this formula, it becomes a simple matter to restore salt and if the kidneys are excreting well, a normal electrolyte structure will result.

*Remove Ketone Acids.*—Salt solution cannot remove ketone acid bodies if they are present. As dextrose is oxidized the ketone acids will be destroyed and removed from the body fluids. It is therefore important to supply dextrose to overcome ketosis as well as to correct renal impairment. As isotonic dextrose liberates more free water it is used in preference to hypertonic glucose.

*Maintain a Normal Fluid and Acid Base Balance.*—As the plasma chlorides are restored and as renal excretion is improved, the patient will show marked clinical improvement. Symptoms will recur if chlorides are lost and dehydration develops. Collier<sup>6</sup> states that at least 4.0 gm. of sodium chloride should be ingested daily in addition to any lost by abnormal routes. The urine output should exceed 2000 c.c. daily. Five hundred cubic centimeters of normal saline each twenty-four hours



THE TIME OF OVULATION IN THE HUMAN FEMALE  
AS DETERMINED BY THE MEASUREMENT OF THE HYDROGEN ION  
CONCENTRATION OF VAGINAL SECRETIONS

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THE marked periodic change in the flora of the vaginal canal together with the cyclic changes in the vaginal smears suggested to us the possibility that the hydrogen ion concentration of the vaginal secretions might have a characteristic menstrual cycle pattern.

Many studies of vaginal secretion pH have appeared. Most of these are the result of an interest in the bacteriology in normal and pathological vaginae.

Behrens and Naujoks<sup>1</sup> reported that the vaginal secretions are quite acid in non-pregnant and pregnant women, and that some pathologic conditions, notably gonorrhea and carcinoma, yield a less acid pH. They reported consistent readings below a pH of 7.0, the range in normal women being from 3.86 to 6.84. No cyclic changes were mentioned. Guthman and Koch<sup>2</sup> reported essentially the same findings. They observed pH's consistently higher than those of Behrens and Naujoks, varying between 5.0 and 7.0. Guthman and Koch also observed that a rise in pH occurred just before the menstrual flow. Oberst and Plass<sup>3</sup> reported that the pH of the vaginal secretions varies directly with the type of bacterial flora present and, therefore, due to the change in flora during the menstrual cycle a corresponding change in pH is to be expected. They also reported that the pH found in different portions of the vaginal canal varies, the secretion from the upper portion (posterior) having a lower value than that of the secretion from the lower portion (anterior).

In the measurement of the pH of these secretions various methods have been employed. Sanssle<sup>7</sup> used litmus paper, Behrens and Naujoks used an electrometric method, Guthman and Koch employed indicators, and Oberst and Plass made use of a microquinhydrone electrode. With the exception of Oberst and Plass who used samples of secretion from definite portions of the vagina, all others used some type of washing for the determinations.

In the present study six normal white women of childbearing age were observed daily for a three-month period, including three complete menstrual cycles. The vaginal washings of the first subject were studied colorimetrically using bromeresol green and chlorphenol red as the indicators. The others were studied using a glass electrode in a Hellige electrometric pH meter. In all subjects, the saliva and urine were also studied from the standpoint of pH changes, the basal body temperatures were taken, smears were made of the vaginal secretions, and any subjective symptoms of ovulation were recorded. In one subject urine samples were extracted and examined for sodium pregnandiol glucuronide.

It was found that a small glass syringe with blunt nose and rubber bulb could be used to inject about 5 c.c. of normal saline into the vagina,

between low plasma chlorides and azotemia, but that the frequent association is brought about by two conditions, vomiting and inadequate urine volume.

A practical treatment should be simple. If the plasma chloride values are known, the amount of salt necessary to restore normal plasma chlorides may be calculated by using Coller's<sup>6</sup> formula. Gamble<sup>3</sup> found that it was unnecessary to use an elaborate solution to replace electrolyte, as all extracellular ions except sodium and chloride ions will be supplied by the metabolic processes even in starvation. To make this possible, the kidneys must be able to control the internal environment with normal efficiency. For this water must be available. Salt may be supplied by the intravenous injection of normal saline. Five per cent dextrose given intravenously will furnish the kidneys with sufficient water to remove retained urine solids, and as the dextrose is oxidized, ketone acids, if present, will be destroyed. Isotonic dextrose is to be preferred as no dangerous symptoms have been noted following its use. Warthen<sup>11</sup> found that no dogs died following experimental infusion of normal saline or 5 per cent dextrose but that frequent fatalities resulted following the use of 10 per cent dextrose. DeLee<sup>12</sup> reported collapse in two cases following the use of hypertonic glucose. After chlorides are replaced and normal renal function is restored, sufficient salt must be given to maintain normal plasma chlorides and sufficient fluid must be ingested to maintain adequate renal function.

The serious symptoms of hyperemesis gravidarum may be entirely due to a disturbed electrolyte structure and dehydration. Many investigators have advised the use of sodium chloride. Coller has developed a clinical rule which permits accurate calculation of the salt deficit. This formula works well in hyperemesis gravidarum; the plasma chlorides may be brought to a normal level in a few hours. This rapid improvement has not been noted if salt replacement is inadequate. The administration of salt solution alone is not sufficient. Glucose and water must be given in sufficiently large amounts to permit restoration of normal renal function. As the kidney function is then unimpaired, excess ions may be excreted. Thus if sodium is given in excess of the body need, the excess sodium may be excreted. Rapid improvement has resulted following this treatment. Clinical improvement may be maintained by supplying an adequate amount of salt and water to satisfy the daily requirement.

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changing the pH value, thus establishing the correctness of the surmise by Oberst and Plass. This observation supports the general supposition that the vaginal secretions are very well buffered. We conclude that the values obtained on the washings represent the average intravaginal condition.

The timing of ovulation by the basal body temperature has been reported by Zuck<sup>9</sup> and, together with our evaluations of smears as described by Papanicolaou<sup>4</sup> and amplified by Rubenstein,<sup>6</sup> give us what we consider the actual period of ovulation in our subjects. In cycles of three of the women subjective signs of follicle rupture were also observed.

The chart (Fig. 1) shows the pH readings of a typical menstrual cycle with correlated basal body temperature, smear evaluation, symptom of follicle rupture as well as pH values of the saliva and urine. Of 18 cycles studied in the 6 subjects, the essential features of this chart were repeated, although 3 cycles did not show such marked pH variations.

It will be noted that during the menstrual flow the pH values rise toward neutrality, and the value obtained varies with the amount of blood present in the flow. In most instances the pH then falls to a value near 4.0 to 4.2 which is maintained with slight variations up to the time of ovulation when a rise occurs to from 4.5 to 5.8. Following this rise the pH returns to the previous level of about 4.0 within twenty-four to forty-eight hours, and is again maintained with slight variations up to the premenstrual day or two, at which time the pH rises and reaches its peak during the first two days of the menstrual flow. In several of our subjects values of 7.0 were recorded during the heavy menstrual flow.

No significant fluctuations in the pH of the saliva or urine were observed so that the pH values of vaginal washings appear characteristic and have no apparent relationship to environmental factors.

It may be significant that the surface tension of the first morning urine shows a marked drop at the midmenstrual period from an analysis of the readings obtained by Perryman and Selous<sup>5</sup> although they did not associate it with the time of ovulation.

In the subject in whom sodium pregnandiol glucuronidate separations were made by the method of Venning<sup>8</sup> it was found in two cycles that the earliest appearance of this substance occurred in the second twenty-four-hour sample of urine following ovulation.

#### CONCLUSIONS

The pH of vaginal secretions shows a rhythmic variation with the menstrual cycle and has a characteristic rise at the time of ovulation.

There is a definite correlation between those changes in ovulation as indicated by vaginal secretion pH and that of basal body temperature and vaginal smear which we have reason to believe (Zuck, 1938) indicate the time of ovulation.

Sodium pregnandiol glucuronidate appears in the urine in the second twenty-four-hour specimen following ovulation. This was determined in two cycles.

and then to withdraw the saline for pH measurements and smear examinations. Saliva was obtained by washing the mouth with about 5 c.c. of saline. The vaginal washings, saliva, as well as a urine sample were obtained shortly after the subject arose in the morning. The rectal temperature was taken at about the same time each day, immediately before arising in the morning.

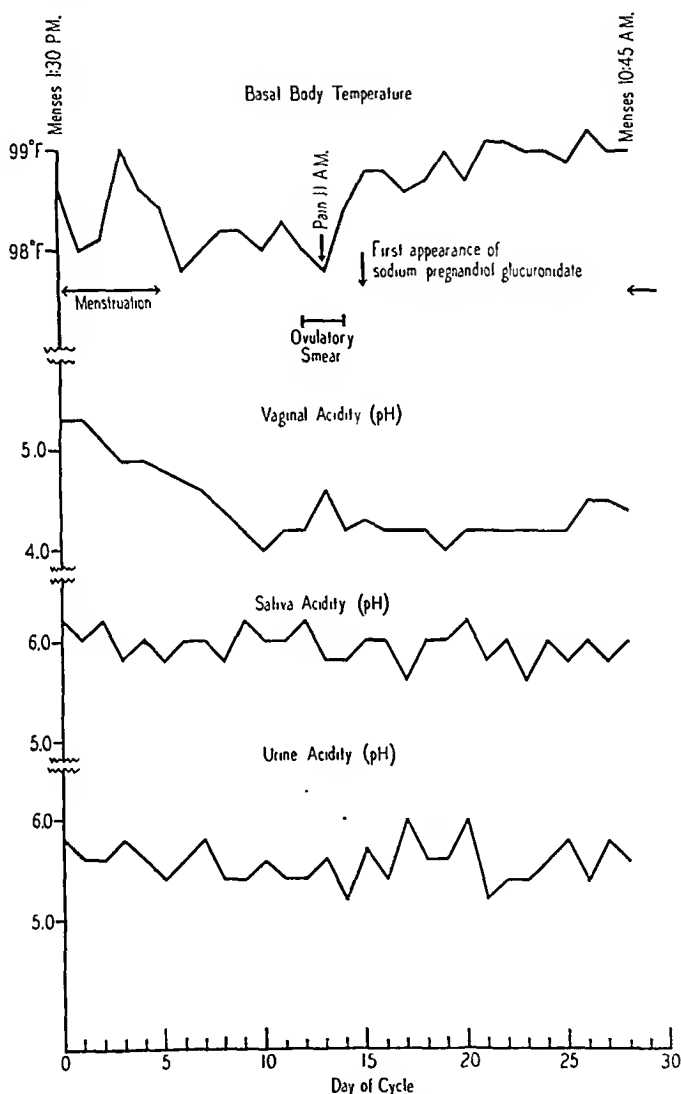


Fig. 1.—The daily record of the rectal body temperature taken before arising is shown at the top. Daily vaginal, salivary and urinary acidity appear as recorded during the menstrual month. The characteristic rise in pH of vaginal washing indicates the time of ovulation.

In the reading of the pH it was found that debris in the washings often caused a slightly higher reading than when the debris was allowed to settle. Thus the readings were always taken after the samples had settled in order to get constant values from determinations repeated over a period of three hours. By separate experiments we found that the saline washing can be diluted with an equal volume of saline without

through masturbation and each specimen was divided into fractions and placed in small cotton-stoppered test tubes. One tube in each case was kept at room temperature while the others were incubated in small separate incubators, specially designed for the purpose, at various temperature levels. The incubators were exact to within one degree centigrade. The tubes were examined throughout the day and night by means of a platinum loop.

At the end of the experiments a mass of figures presented itself. No two cases were found to be alike. However, there was a surprising accordance of figures when allowed to be fitted into a normal range (Fig. 1). As was expected all the specimens at room temperatures showed optimal vitality. With increases of temperature, spermatozoal life became shortened. At 37° C. (body temperature) the average specimens endured from eight to ten hours, whereas at higher temperatures the spermatozoa died much more rapidly. The spermatozoa only lived from four to six hours at 41° C., while at 45° C. they were practically nonresistant.

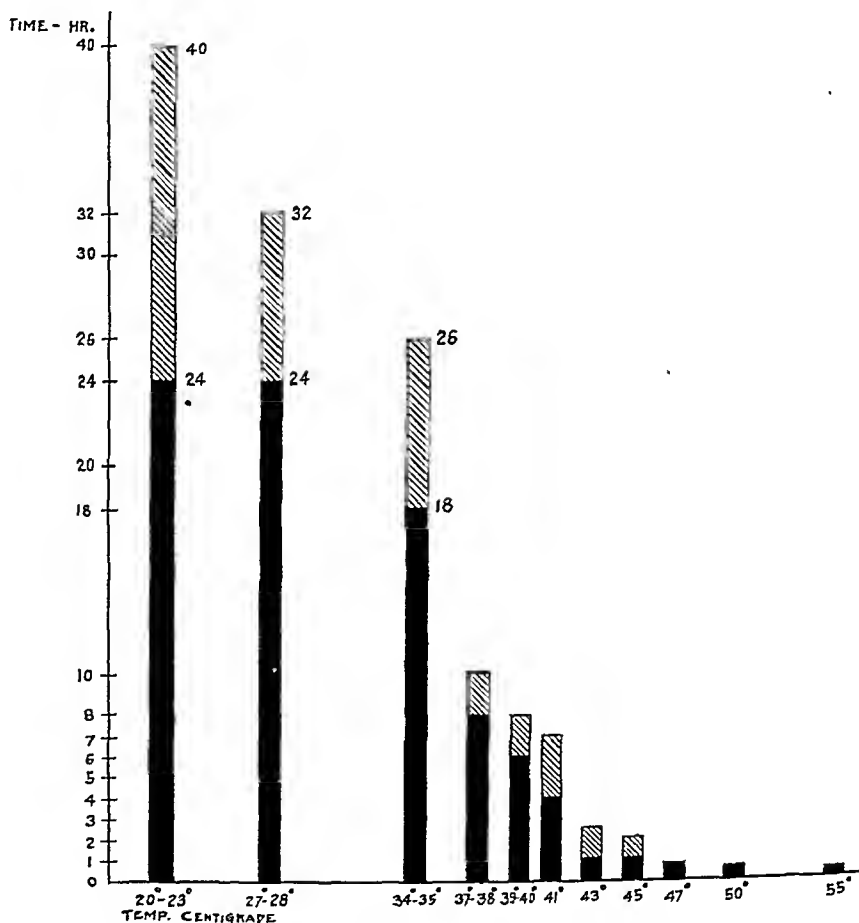


FIG. 1 EFFECT OF TEMPERATURE ON LONGEVITY OF SPERMATOZOA.

AREA REPRESENTS THE VARIATIONS MOST USUALLY FOUND.

Fig. 1.

## DISCUSSION

Having obtained such uniformly similar results when testing normal spermatozoa for resistance to definite elevations in temperatures, I am now using these temperature reactions as part of my routine spermatozoal analysis. In general, if the seminal fluid conforms to most of the

The pH values of urine and saliva show no cyclic variations in women.

The measurement of vaginal pH in our opinion affords a new method of timing ovulation.

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2109 ADELBERT ROAD

## THE EFFECT OF TEMPERATURE UPON THE VITALITY OF SPERMATOZOA

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IT IS accepted by Moench,<sup>1</sup> Belding,<sup>2</sup> and Hotchkiss, Brunner and Grenley<sup>3</sup> that the ideal temperature for viability of human spermatozoa outside the body is below room temperature and somewhere between 20° and 8° C. In a previous paper, I corroborated their findings, that spermatozoa live longer at lower temperatures than at higher temperatures.<sup>4</sup> However, spermatozoa in the course of their physiologic wanderings inside of the female never or rarely encounter lower temperatures than 37° C. The natural environmental temperature even in the scrotum rarely drops much below 37° C. Therefore to study motility, reaction to acidity, etc., of human spermatozoa at 8 to 20° C. or at room temperatures is not pursuing the study under physiologic or near physiologic conditions, and is comparable to studying the sex life of an Eskimo while in the tropics.

Human spermatozoa should be studied at body or scrotal temperatures in order to obtain a resulting truer picture. In testing for motility, viability, and endurance of human spermatozoa outside of the body, it would seem more logical to test their responses at their physiologic temperatures rather than at some subnormal temperature. Moreover, since it is accepted and recognized that spermatozoa are more resistant to cold than to heat, the endurance, motility, etc., should be studied at elevated temperatures rather than subnormal temperatures. A more exact physiologic status of the strength and resistance of the male elements can thus be obtained.

#### EXPERIMENTAL

Twenty-four young virile men between the ages of 20 and 38 were studied.\* In most cases repeated examinations were performed. Seminal specimens were obtained

\*The subjects included volunteer medical students, physicians, and private patients not complaining of sterility.

of the skin and very slowly and without using undue force, 0.1 c.c. of the control solution is first injected. The bleb so produced should be circular, and should present a typical pitted "orange peel" surface. In this series of cases, five minutes were allowed to elapse before the test solution was injected. If no pseudopodia were formed at the site of injection of the control test in this period of time, it was assumed that this patient was suitable for the use of pregniotin.

One-tenth cubic centimeter of test solution is then injected in a similar manner in a parallel location. If the reaction is positive, pseudopodia appear in one to four minutes, originating in the margin of the bleb. Within another ten minutes the entire reaction will have faded. If the reaction is negative, pseudopodia do not appear; the bleb remains circular and gradually regresses. The presence or absence of erythema is of no significance. The test should not be performed under artificial light, as pseudopodia, easily visible in daylight, may not otherwise be detectable.

The Gruskin test for pregnancy is said not to be applicable to patients who are jaundiced or have elevated temperatures. In patients who have received x-ray or radium treatment, two weeks are allowed to elapse before this test is applied. Patients who have been operated upon should not be tested until the incision is healed completely.

Gruskin<sup>2</sup> has reported results on a series of patients on whom the test was used under clinical supervision of Dr. J. O. Arnold at Temple University. In this series there were 162 correctly positive reactions, and 8 incorrectly positive reactions. The latter occurred in patients later found to be suffering from teratoid carcinoma or hydatidiform mole. There were 11 correctly negative reactions, 3 in the presence of carcinoma and of cervical erosions.

Schwartz<sup>3</sup> reported 221 cases in which the Gruskin test was employed. Correct diagnoses were arrived at in 209, or 94.6 per cent, and incorrect diagnoses in 12, or 5.4 per cent.

Pregniotin differs from the other materials<sup>4, 5</sup> used in cutaneous tests for pregnancy; the latter employ gonadotropic extracts of pregnancy urine, placenta, or pituitary. Pregniotin contains no gonadotropic substance. In the use of the gonadotropic extracts a positive reading is made when no cutaneous response is obtained. In the use of pregniotin a positive reading is made only when pseudopodia are found.

## RESULTS

In our series reported here, 48 tests were made. Of these, 42 were females and 6 were males. The 42 females ranged in age from 18 to 48, with the greater number in the 18 to 30 age group. There were 11 patients who had had no children, 16 who had 1, 5 who had 2, 5 who had 3, and 5 who had more than 3. Of these 42, 22 were known to be pregnant clinically. Pregniotin gave positive tests in 21 of these 22 cases. The one negative result occurred in a patient who was six months pregnant, who had a positive Kline test and was under treatment for syphilis. Seven post-natals were tested, from one to thirteen days post partum. In all these cases the test was positive.

Three patients were examined for diagnosis:

1. Amenorrhea of two months. Obesity made a clinical diagnosis difficult. Pregniotin test was positive. The diagnosis of pregnancy was later confirmed clinically.

2. Pregnancy suspected because period was ten days overdue. Pregniotin test was negative. Examination revealed a lutein cyst.

3. Ectopic pregnancy suspected on basis of history. Pregniotin gave a positive result. Friedman test performed the same day was negative.

A series of 10 additional patients having the following gynecologic conditions, but having no clinical evidence of pregnancy, were likewise tested.

1. Chronic cervicitis and a retroplaced uterus. Pregniotin test negative.

other requirements of normalcy, the spermatozoa almost always endure for twenty-four to thirty-six hours at room temperature, and for eight to ten hours at body temperature, and for at least four hours at 41° C.

In the small series of cases tested so far, if I find that the spermatozoa in a specimen cannot endure room temperature for twenty-four hours, and body temperature for eight hours and 41° C. for at least four hours, then concurrent pathologic findings such as excessive abnormal forms, diminution in number, etc., are the rule.

#### SUMMARY

Human spermatozoa should be studied for motility and endurance, etc., at temperatures closely approximating their physiologic body temperature. Subnormal temperatures used to keep spermatozoa alive for longer periods of time do not reveal the true physiologic picture. The effect of elevated temperatures upon human spermatozoa was studied with the evolution of a scale illustrating the normal longevity of spermatozoa at definite temperature levels.

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## THE PREGNIOTIN TEST FOR PREGNANCY

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THE Arnold-Gruskin<sup>1</sup> test is a cutaneous test for pregnancy devised and developed by Dr. Benjamin Gruskin of Temple University. The substance used in our investigation is an antigen made from human placenta by E. R. Squibb & Sons, and distributed for experimental purposes under the name of "Pregniotin."

The test is an intradermal one. A positive reaction is evidenced by the appearance of pseudopodia. If pseudopodia fail to appear, the test is negative. Before testing with pregniotin each patient receives an injection of a control solution supplied with each package. This control solution, prepared from the amniotic membranes, is injected in exactly the same manner as the test solution itself, except that a separate sterile tuberculin syringe and needle are used. Any patient who shows a positive pseudopodic reaction to the control solution is not suitable for testing with pregniotin.

The technique as prescribed by the manufacturer is as follows: The skin of the forearm is cleansed gently with alcohol and dried with sterile gauze, care being taken to avoid producing erythema. Pregniotin and the control solution are drawn up in separate tuberculin syringes. The needle is inserted in the stratum spinosum layer



# THE CONTROL OF PAIN WITH LOCAL ANESTHESIA AFTER THE REPAIR OF EPISIOTOMIES\*

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REPORTS of the successful use of soluble anesthetic solutions in rectal surgery with the purpose of relieving patients from post-operative pain have suggested the use of this type of medication following episiotomy and other perineal repair. The more or less widespread use of analgesia in labor has left the post-partum pain incident to perineal repair the most distressing factor of delivery and the puerperium.

This is merely a preliminary report on a small series of 25 patients with 25 alternate patients taken as controls. The results were so encouraging that it was deemed advisable to publish them. Two types of solutions were used, one an oil soluble solution of the following formula: Procaine base 1.5 per cent, butesin 6 per cent, benzyl alcohol 5 per cent, and oil of sweet almond q. s.; the other, an aqueous solution containing 1 per cent piperidinopropanedio di-phenylurethane hydrochloride.

## TECHNIQUE OF ADMINISTRATION

Following repair of the episiotomy or perineal laceration 10 c.c. of the solution are withdrawn from the previously warmed bottle (110° F.) into a dry Luer Lok syringe. The skin of the area to be injected is thoroughly cleansed and an antiseptic applied. The solution is then injected slowly into the deeper tissue taking care that it does not go immediately beneath the skin or mucous membranes as it may result in sloughing. Following injection, massage of the parts assures an even distribution of the anesthetic and prevents pooling. The needle is inserted about  $\frac{1}{4}$  inch on either side of the incision and the medicine then injected fanwise. The injection is made while the patient is still under the effects of the general anesthesia given during repair.

## RESULTS

Patients were questioned regarding perineal discomfort upon awakening and on each post-partum day until discharge from the hospital. The variable factor or individual response to pain is definitely considered in evaluating the record. The water soluble solution was used in 10 cases. These patients were free from pain until the third or fourth post-partum day, at which time the effects of the anesthesia had apparently disappeared. They then experienced as much pain as the controls. The oil soluble anesthetic, however, kept patients for the most part entirely free from distress. Some degree of anesthesia remained in a few cases for as long as three weeks following delivery. The patients in whom no local anesthesia was used complained of varying degrees of distress, some of which was so intense that the application of anesthetic ointments or the use of analgesic suppositories per rectum was required.

In the series of 25 cases and 25 controls, healing did not appear to be impaired except in one instance. In this case there was a breakdown of the episiotomy wound requiring secondary suture. There had been noted an infected cervix, which could

\*The butecaine was furnished by the Abbott Company.

2. Hysterectomy for pelvic inflammatory disease, seven weeks previous to test. Pregniotin test positive.
3. Pruritis vulvae being treated in the endocrine clinic. Pregniotin test negative.
4. Chronic cervicitis. Pregniotin test negative.
5. Fibrosis uteri and chronic cervicitis. Pregniotin test negative.
6. Multiple uterine fibroids. Pregniotin test negative.
7. Functional menorrhagia. Pregniotin test negative.
8. Functional menorrhagia with cervicitis. Pregniotin test negative.
9. Pelvic inflammatory disease, not operated on. Pregniotin test negative.
10. Chronic cervicitis. Pregniotin test negative.

Of the 6 males, ranging in age from 28 to 40, the first 4 were tested early in our series and all gave negative reactions. The last 2 were tested about four weeks after the expiration date of the experimental antigen supplied to us by E. R. Squibb & Sons. Both of these tests were positive. Each of the patients experienced pain and burning at the site of the injection, where a large wheal was formed. These false positives were probably due to deterioration of the antigen.

In no case in this series was a positive reaction obtained at the site of the control injection.

#### SUMMARY

1. A series of 48 patients were tested with pregniotin, an antigen prepared from human placenta for intradermal injection to determine pregnancy.

2. Pregniotin gave a positive reaction in 21 out of 22 patients known to be pregnant.

3. Seven patients, tested postnatally from one to twelve days post partum, all gave a positive reaction.

4. Six males were tested, 4 being negative and 2 positive. The 2 false positives were considered to be due to the deterioration of the product. No opportunity was afforded us of checking these results with a fresh product, as it was no longer available from the manufacturer.

5. Three patients examined for diagnosis by this test gave 2 correct results and 1 false.

6. Ten patients definitely not pregnant were tested, with 9 correct results and 1 false positive.

#### CONCLUSIONS

Pregniotin appears to be the best of all the skin pregnancy tests.

It does not, however, compare favorably with the Friedman modification of the Aschheim-Zondek test.

For a rapid, tentative diagnosis, pregniotin may prove useful, but results of this test should be checked by the Friedman method.

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## HEART BLOCK AND PREGNANCY

### REPORT OF A CASE, WITH ELECTROCARDIOGRAPHIC OBSERVATIONS DURING CESAREAN SECTION UNDER CYCLOPROPANE ANESTHESIA

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THE following case is presented because of the unusual association of conditions. The number of reports of the occurrence of heart block and pregnancy is so small that additional observations on this association merit considerable study. A review of the literature reveals 13 reports of 15 cases.<sup>1-13</sup> Because of the scarcity of material the physician is confronted with a difficult problem in the handling of patients who present both these conditions.

In all but a few of the reported cases electrocardiograms have been taken before and after delivery, but so far as is known this is the first instance in which electrocardiograms have been taken during cesarean section.

#### CASE REPORT

The patient, E. L., white female, 33 years of age, housewife, pregnant for eight months, was admitted to the Mount Vernon Hospital on March 10, 1936, because of premature rupture of the membranes.

Her previous history was of considerable importance and interest, and the following were the essential facts. In childhood she suffered with measles, mumps, pertussis, and chicken pox. Tonsillitis occurred about twice a year between the ages of 18 and 22. In 1930 she came to this country from Ireland and was examined by immigration physicians, no defects being found then. Her menses began at 13 and have been regular. She has been married for six years and her husband has been in good health. In October, 1931, she became pregnant for the first time and attended the prenatal clinic at the Mount Vernon Hospital. She felt well until about May 1, 1932, when she began to develop symptoms and signs of eclamptic toxemia. In spite of rest in bed and routine treatment her blood pressure rose sharply. The signs of toxemia increased and the patient was admitted to the hospital on June 4, 1932. A four-and-one-half-pound premature baby was delivered which failed to survive the first twenty-four hours. At the time of admission to the hospital it was noted that the patient had a cardiac arrhythmia. On physical examination she presented definite signs of mitral stenosis and insufficiency with auricular fibrillation. No electrocardiogram was taken until five days later when the heart became very slow and regular. A record then showed complete auriculoventricular dissociation. The patient remained in the hospital until July 1, 1932, her convalescence being marked by a thrombophlebitis of the right long saphenous vein. After discharge from the hospital she made a slow but steady recovery, her blood pressure gradually becoming lower and the urine returning to normal. From time to time she experienced some precordial pain. Her menstrual periods were resumed in November, 1932. By April, 1934 the patient felt quite well and was able to carry on all her household duties without any signs or symptoms of cardiac insufficiency. Frequent electrocardiograms taken since 1932 showed a persistence of the heart block.

Her family history revealed that her father who is 65 years of age has hypertension. An uncle has a "bad heart."

*Present History.*—In September, 1935 the patient presented herself again, reporting that she had become pregnant. Her last menstrual period occurred on June 28, 1935. She was kept under constant observation during the antenatal period and bore the pregnancy extremely well. On March 10, 1936, approximately one month before term, her membranes ruptured spontaneously and she was admitted to the Mount Vernon Hospital immediately.

not be treated adequately during pregnancy. The patient also had a mild post-partum pyelitis with positive *B. coli* urine culture. It would seem that one should not attempt the use of the infiltration in a situation such as this. Others, writing on the use of this procedure in rectal work, have stressed the inadvisability of using the solution in the presence of possible infection. There were no individual reactions or tissue sloughs; nor was there any delay in the healing of the wounds. In no case were there any general toxic effects noted.

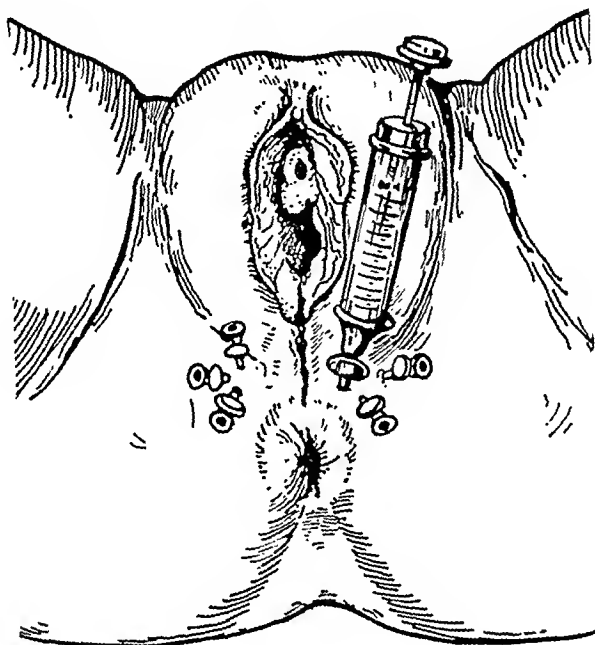


Fig. 1.

#### CONCLUSIONS

The results in this small series are very encouraging. With the more or less widespread use of analgesia in labor and with the desire of obstetricians to make labor and the puerperium as free as possible from distressing symptoms, it would seem that the use of slowly absorbing anesthetic solutions in repairs is a valuable adjunct to the obstetric armamentarium. The more slowly absorbed oil solutions appear from this study to be superior to the water soluble preparations. The presence of infection is a definite contraindication to the use of this type of procedure.

This being merely a preliminary study, a further evaluation will follow the continued use of the adjunct on a larger series of patients at some later date.

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firm union of the wound, temperature ranging around 99° F., pulse around 50, blood pressure 150/70. The heart revealed sounds of good quality, the murmur heard before operation having disappeared.

Frequent examinations, both clinical and electrocardiographic, have been made since the patient left the hospital. Up to the present time, two years after operation, there have been no changes in the patient's condition. Her cardiac reserve is excellent and electrocardiographic tracings show the same mechanism as before delivery.

#### DISCUSSION

Lennox, Graves and Levine<sup>15</sup> who were among the first to record electrocardiographic tracings on patients during operation, stated that in order to understand the function of the heart it would be very important to study it during periods of stress. Our patient admirably presented such an opportunity, especially in view of the pre-existing disturbance of rhythm. It is difficult, however, to be certain that there is any one factor which is responsible for the changes recorded. In order to draw definite conclusions as to cause and effect, a large number of cases will have to be studied, varying only one factor at a time. Kurtz, Bennett and Shapiro<sup>14</sup> likewise encountered considerable difficulty in determining whether the surgical procedure or the anesthesia itself was the most important factor in the production of the disturbances which they recorded. In the series of the latter, the electrocardiographic tracings of their Case II appear to be identical with those which we obtained at 12:40, 12:52, 12:56, and 1:05.

It is known that two types of mechanism are found during Stokes-Adams seizures; one is complete ventricular standstill, the other ventricular fibrillation. The fascinating studies of Schwartz and Jezer<sup>18, 19</sup> have brought out some unusually interesting facts in this regard. Study of our records makes one wonder how far removed from ventricular fibrillation our patient might have been. However, it may be stated that in spite of the appearance of the records, the patient's condition on the operating table was never alarming, and at the completion of the operation it was as satisfactory as before.

Fig. 1 shows the electrical activity of the heart throughout the entire operative procedure. The development of the extrasystolic tachycardia and the auricular flutter in the presence of heart block is unusual and they are extremely important phenomena to report. It is to be hoped that more cases of this type will be described in the literature.

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*Physical Examination.*—Temperature 99° F., pulse 48, respiration 20, blood pressure 170/80. Examination of the heart revealed the apex impulse in the fifth left intercostal space in the midclavicular line; no shocks or thrills palpable. The first sound at the apex was obscured by a loud rough systolic murmur. The lungs were clear. The fundus was about four fingerbreadths below the xiphoid. By abdominal palpation a diagnosis of left occiput anterior was made, with head floating. No vaginal examination was made. There were marked varicosities of the vulva and lower extremities.

*Course in Hospital.*—On consultation with Dr. William T. Liccione it was decided that because of the heart block it would be more expedient to perform a cesarean section than to risk a prolonged dry labor in a patient who had had a toxemia, and who now had an organic though asymptomatic heart lesion.

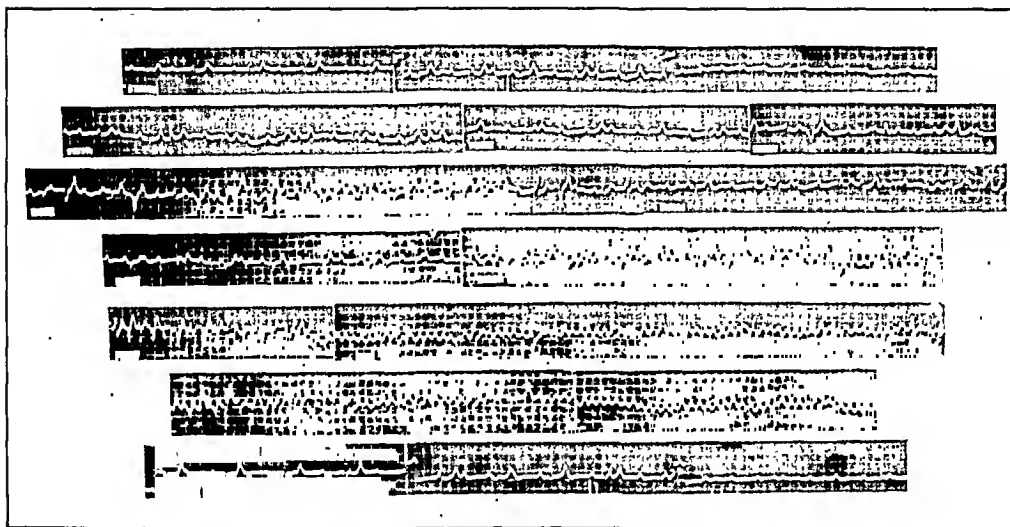


Fig. 1.—Shows record before, during, and after operation. At the top is seen three conventional leads of the control record; then a series of strips taken during operation using Lead II only. At the bottom is seen three conventional leads taken twenty-four hours after operation. The time each strip was taken is noted. 12:25, Control record, complete A-V dissociation, auricular rate 100, ventricular 50. 12:30, Occasional premature beat. 12:36, Premature beats from more than one focus. 12:40, Bigeminy, followed by ventricular extrasystolic tachycardia. 12:43, Premature beats. 12:47, A-V dissociation, ventricular rate 55. 12:52 and 12:56, Extrasystolic tachycardia. 1:00, Auricular flutter, premature beats. 1:05, Extrasystolic tachycardia, followed by flutter. 1:08, Auricular flutter.

The patient was examined by Dr. Wilmer S. Wilson, who decided to use cyclopropane anesthesia, first, because of the possibility of administering a high concentration of oxygen, and second, because of its assistance in contracting the uterus after the placenta is removed. As a preliminary, 3 gr. of pentobarbital were administered.

Low cesarean section was performed by Dr. William T. Liccione. The anesthesia was started at 12:27; the incision made at 12:37; the fetus delivered at 12:42; the operation completed at 1:15 A.M. During the course of the operation frequent electrocardiographic tracings were taken. These are shown in Fig. 1.

On leaving the operating table the patient showed some cyanosis which persisted for twenty-four hours. The pulse rate varied between 40 and 60. The further course was marked by the occurrence of low grade fever, due to thrombophlebitis, which began about three days postoperatively and lasted for about two weeks, running between 99° and 101° F. The patient, however, was free of symptoms and merely showed the presence of a small thrombus in the left long saphenous vein and one in a vein on the left side of the vulva. These disappeared within three weeks. Two weeks postoperatively the patient was sent home, and one week later was permitted out of bed. Examination three weeks postoperatively revealed

*Physical Findings.*—Marked pallor and weakness and purpuric skin manifestations, present in areas previously mentioned, characterized the general picture. A bilateral chronic otitis media was found; and through a large central left eardrum perforation a foul-smelling, thin discharge escaped. The mastoid sear was also noted. Nasal and gingival bleeding was active.

The abdomen, enlarged by a uterus reaching just above the umbilicus, indicated a six months' gravidity. Intrauterine activity and normal heart sounds attested fetal viability. The spleen was slightly enlarged.

The blood study (Dr. Nathan Rosenthal), which follows, confirmed the tentative clinical diagnosis of thrombocytopenic purpura with secondary anemia. Platelets 10,000; hemoglobin, 45 per cent; red blood cells, 2,790,000; white blood corpuscles, 12,000; polymorphonuclear leucocytes, 80 per cent, nonsegmented, 71 per cent, segmented, 9 per cent; eosinophiles, 2 per cent; basophiles, 1 per cent; lymphocytes, 9 per cent; monocytes, 8 per cent. Hematocrit, 21 per cent; reticulocytes, 2.5 per cent. Bleeding time: over 10 minutes; coagulation time, 13 minutes; tourniquet test, positive.

The cytologic study of the bone marrow aspiration was essentially normal except for a slight increase in megalokaryocytes. Cell count, 250,000; megakaryocytes, 13.2 per cent; myeloblasts, 1.4 per cent; myelocytes, 29.4 per cent; polymorphonuclear leucocytes, 48.8 per cent, nonsegmented, 28.6 per cent, segmented, 20.2 per cent; lymphocytes, 1.0 per cent.

Urine: Specific gravity 1.018; reaction, acid; albumin, faint trace; sugar, negative; 25 white blood cells and a few red blood cells per high power field: occasional clumps of epithelial cells.

Blood chemistry: Sugar, 100 mg. per cent; urea nitrogen, 8 mg. per cent; cholesterol, 275 mg. per cent; total protein 5.5 mg. per cent. Wassermann and Kahn tests, negative.

The patient received during the first week several blood transfusions (500 c.c. each), and the hemoglobin rose to 57 per cent. Daily increasing doses of moccasin snake venom were injected intracutaneously (0.1 c.c. to 0.4 c.c.).

General bleeding persisted, however; the spongy gum margins continued to ooze and began to manifest purulent changes. To interrupt the gravidity at this stage was considered inadvisable, since it interposed the hazard of hemorrhage and yielded no advantage. The patient's general condition did not improve.

Further temporizing was contraindicated and splenectomy was therefore immediately performed on March 21, 1938, by Dr. John Garlock, under avertin-ethylene anesthesia. Oozing from the pedicle and residual strands of adhesions necessitated drainage. Sutures were removed from the firmly healed subcostal wound on the ninth day.

The pathologic study of the spleen was reported by Dr. Paul Klemperer as follows: Weight 130 gm., size 15 by 8 by 4 cm. Hyperplastic pulp with many eosinophilic myelocytes; Malpighian corpuscles numerous and conspicuous.

Postoperatively, the patient gained strength quickly. The skin purpura disappeared gradually, and no new lesions were evident. Her blood count revealed striking improvement, showing a platelet increment from 10,000 to 220,000. Red blood cells, 3,600,000; white blood cells, 9,900; hemoglobin, 65 per cent; polymorphonuclear leucocytes, 82 per cent, segmented, 63 per cent, staff, 19 per cent; myelocytes, 1 per cent; lymphocytes, 14 per cent; monocytes, 3 per cent.

The brighter general appearance, the cessation of the vaginal, nasal, and gingival hemorrhage, and the improved postoperative picture indicated abatement of the disease.

On April 7, seventeen days after operation, without any apparent ill effects from the splenectomy, the patient was discharged. Her blood picture remained normal and fairly constant. Obstetric observations were within normal limits, the pelvis being ample upon both external and internal mensuration. Fetal heart was between 130 and 140.

The blood study on May 3, 1938, was as follows: Platelets, 147,000 (a few giant platelets); red blood cells, 3,690,000; hemoglobin, 66 per cent; white blood

# THE PROBLEM OF IDIOPATHIC PURPURA HEMORRHAGICA IN PREGNANCY AND THE NEONATAL PERIOD

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**T**HROMBOCYTOPENIC purpura occurs either as an idiopathic entity or as a symptomatic manifestation of blood dyscrasia, infection, exogenous or metabolic intoxication or secondary to malignancy.

The essential or idiopathic form first described by Werlhof<sup>35</sup> in 1775 is now regarded as dependent upon either (1) a primary defect in platelet formation (megakaryophthisis), (2) a pathologic destruction of platelets in the spleen, or (3) a qualitative disturbance in the platelets themselves.

The conduct and outcome of a pregnancy complicated by this disease is always problematical. Although splenectomy in definitely indicated cases improves the prognosis, the actual effects of purpura hemorrhagica upon the state of gravidity are uncertain.

Purpura in pregnancy and puerperium was first observed in 1765, but not until the establishment of the etiologic classification was proper attention directed to the morphology and coagulation of blood, as well as the capillary physiology. Mosher,<sup>17</sup> Rushmore,<sup>28</sup> and Pingat,<sup>21</sup> published clinical reports of this condition in pregnancy. More recently, Liebling<sup>14</sup> and Waltner,<sup>34</sup> described purpura in children born of thrombocytopenic mothers, but there is a dearth of completed records of this disease in the literature.

Pediatricians ascribe purpura in the newborn to heredity, while the obstetric writings subscribe to a congenital etiologic basis.

This report concerns itself with a severe idiopathic form of purpura hemorrhagica. Not only are clinical aspects presented but also a complete hematologic study of an infant, and its purpuric mother, before and after delivery. In addition, the surgical therapy (splenectomy), the striking absence of post-partum hemorrhage and the complete recovery of the mother are of an interest unusual enough to warrant the presentation of this rare condition.

G. R. (No. 42157), a 23-year-old primipara in the fifth month of pregnancy, entered Mt. Sinai Hospital on March 14, 1938, because of a four-day episode of continuous vaginal hemorrhage and a "gushing" epistaxis.

Menses (12x30x3) were always normal and regular, accompanied by slight dysmenorrhea. A chronic, discharging, bilateral otitis media with subsequent deafness resulted from an attack of measles, and four years ago a left mastoidectomy was necessary. Since then frequent treatments for exacerbations of sinusitis and otitis required medical attention.

Seven months ago the patient had nausea, vomiting, chills, and fever (104° F.) of unknown etiology, which disappeared after one week of treatment with sulfanilamide and iron capsules. Two months later she became pregnant (last menstrual period Oct. 7, 1937).

In the early weeks of pregnancy, large areas of ecchymosis on the upper chest and lower extremities appeared for the first time. Later smaller coalescent groups of similar character were observed on the arms. During the third month of pregnancy vaginal staining occurred for one day. The hemoglobin at this time (Tallqvist) was 70 per cent. The purpuric lesions persisted but there was no active bleeding. Medication did not include coal tar, gold, arsenical, benzol derivatives or other heavy metals; nor was x-ray or radium used. Iron supplemented by ABD vitamin capsules was the only therapy administered.



cent; eosinophiles, 2 per cent; myelocytes, 1 per cent; reticulocytes, 6.9 per cent; (normoblasts 10 per high powered field); bleeding time,  $3\frac{1}{2}$  minutes; coagulation time,  $4\frac{1}{2}$  minutes.

The slight edema of the pubic region, pelvis, and lower extremities which appeared on the second day was accounted for by posture (Fowler's position), rather than on the basis of a blood dyscrasia, since there was no jaundice or anemia, and also since the erythroblastemia disappeared before the seventh day of life. Six days after birth cyanotic spells appeared after feeding, and on the following day  $O_2$  and  $CO_2$  therapy was required. The baby took its feeding poorly, or not at all, and the temperature began to rise. Signs of atelectasis were discernible in the chest, and the day following (May 20) the infant was constantly and deeply cyanosed, notwithstanding continuous oxygen administration. Feeding was stopped and clysis substituted. The respirations that day became irregular, and at both bases of the lungs posteriorly, breath sounds could not be elicited. On the evening of May 20, eight days after birth, the baby died.

On post mortem examination (Dr. Freund), in addition to the usual anatomic evidence of prematurity (sparse subcutaneous fat, etc.), both lungs were found to be noncrepitant throughout and sank immediately when placed in water; the cut surface showed characteristic appearance of collapse. It is of interest that anatomically the spleen was entirely normal, as were the bone marrow, liver, etc. There was a small area of hemorrhage in the right apical visceral pleura of the lung and small mucosal hemorrhages in the jejunum, ileum, and bladder mucosa, all of which were interpreted as agonal.

#### CONCLUSIONS

1. An obstetric problem, in which a gravidity was complicated by purpura hemorrhagica, is presented.

2. Following splenectomy, the maternal blood morphology became normal, remaining so throughout the entire period of gravidity, as well as after delivery.

3. Of great importance is the fact, that the blood picture of the newborn also was entirely normal. In addition, post mortem examination (death due to pulmonary atelectasis) revealed no pathologic disturbances of the hematopoietic system.

4. We conclude that a newborn infant will be free of this disease, if delivered of a purpuric mother, if her blood picture, following splenectomy, reveals complete remission.

5. Contrariwise, however, the literature establishes that the disease is congenital when, despite splenectomy, the hematologic characteristics of purpura are found in the blood of the mother.

6. Furthermore, the question presents itself as to the role splenectomy played in the premature onset of labor (endocrine imbalance).

7. In addition, since there was essentially no blood loss at delivery, the thought arises as to the effect of splenectomy on post-partum hemorrhage.

8. The role of the spleen in the gravid patient remains to be determined. Such cases as above described, present opportunity for this study. Comparative observation of pregnancy in patients with and without their spleen may reveal its mechanism in pregnancy.

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cells, 14,000; polymorphonuclear leucocytes 73 per cent, staffs, 8 per cent; eosinophiles, 1 per cent; lymphocytes, 10 per cent; monocytes, 6 per cent; metamyelocytes, 2 per cent.

Two months prematurely uterine contractions spontaneously set in, and on May 12, at Beth Israel Hospital, after a ten-hour labor, the patient delivered normally. Although all necessary emergency measures were in readiness in anticipation of hemorrhage, they were not required since unexpectedly the blood loss incidental to delivery totalled only 30 c.c.

The post-partum course was uneventful. Involution of the uterus took place in the usual manner, and no further manifestations of the bleeding diathesis were observed. Daily post-partum blood counts were all normal.

Forty-three days after delivery the blood picture was still unchanged: Platelets, 180,000; red blood cells, 4,500,000; hemoglobin, 80 per cent; white blood cells, 9,600; polymorphonuclear leucocytes, 66 per cent; lymphocytes, 30 per cent; monocytes, 4 per cent.

The patient is completely well now (eight months post partum), and has been advised that no contraindications to a future pregnancy are believed to be present, since all blood studies during the period following delivery were normal.

As relates to the offspring of gravid patients with thrombocytopenic purpura, comparatively little is known. In fact, case reports are relatively few, testifying to the rarity of the condition.

Of poignant interest are the recent reports on the congenital aspects of this condition. Greenwald and Sherman,<sup>11</sup> in 1929, described an insufficiency of megalokaryocytes in the bone marrow of the offspring. The morphology of the maternal blood was not studied, however.

Sanford, Leslie and Crane,<sup>29</sup> in 1936, observed marked thrombocytopenia and increased disintegrative power of the platelets in both mother and newborn infant.

Davidson's<sup>7</sup> interesting paper, in 1937, describes a remission during a pregnancy eight and one-half years after splenectomy (epistaxis, skin purpura, platelets always between six and 47,000, and severe post-partum hemorrhage). The infant at birth had a severe hemorrhage and a low platelet count.

In our studies of the infant, totally different findings obtain. The clinical, blood and pathologic studies confirm conclusively the absence of purpura hemorrhagica. A complete description of the seven months' premature newborn infant, delivered fifty-three days following splenectomy of the mother, is presented.

The infant was a male, weighing three pounds, and living at birth. Its skin presented the characteristic dearth of subcutaneous fat as seen in prematurity, and was covered with normal colored vernix caseosa. There was no icterus of the skin or sclerae, and no cutaneous or mucosal purpura. The head showed no evidence of molding, no cephalohematomas were present. Respiration at birth was spontaneous, requiring no artificial means to initiate or maintain. The heart sounds were normal; rhythm regular, and rate normal. Breath sounds were heard throughout the pulmonary fields. The cry was feeble but not delayed. The abdomen showed no evidence of ascites, or masses. No congenital malformations of the mouth or palate were noted. The anus was perforate. Special incubator care was provided.

Blood count, on the first day of life, showed: Platelets, 170,000 (few giant platelets); red blood cells, 4,540,000; hemoglobin (Sahli), 122 per cent; color index, 1.3 per cent; white blood cells, 12,650; polymorphonuclear leucocytes, 68 per cent, staffs, 18 per cent, segmented, 50 per cent; lymphocytes, 23 per cent; monocytes, 8 per cent; myelocytes, 1 per cent; normoblasts, 7 per 100 white blood cells.

Ten cubic centimeters of blood was given intramuscularly, and during the first twenty-four hours the color remained good and the cry became stronger. Occasionally small amounts of breast milk regurgitated, but the next day feedings were well taken. The baby voided freely and passed meconium stools.

The blood count on the third day remained essentially as at birth, showing: Platelets, 167,000; red blood cells, 4,490,000; hemoglobin, 114 per cent; color index, 1.2; white blood cells, 11,900; polymorphonuclear leucocytes, 70 per cent, staffs, 9 per cent, segmented, 61 per cent; lymphocytes, 20 per cent; monocytes, 7 per

*Course.*—Right chest aspirated, 2,000 c.c. serosanguinous fluid removed. Smear, no organisms. Culture sterile. Revolta positive. Guinea pig inoculated and on autopsy revealed no evidence of tuberculosis. Chest fluid smear: fibrin, many red blood cells, lymphocytes, monocytes and few polymorphonuclear cells. Occasional epithelial cell. No neoplastic cells noted.

X-rays of pelvis, skull, ribs, femoral necks, and of gastrointestinal tract including a barium enema showed no radiographic evidence of metastasis.

X-ray of chest after removal of 2,000 c.c. of fluid revealed two dense areas of opacity in the base of the right lung which were suggestive of the presence of metastatic malignancy. The presence of localized collections of residual fluid must also be considered.

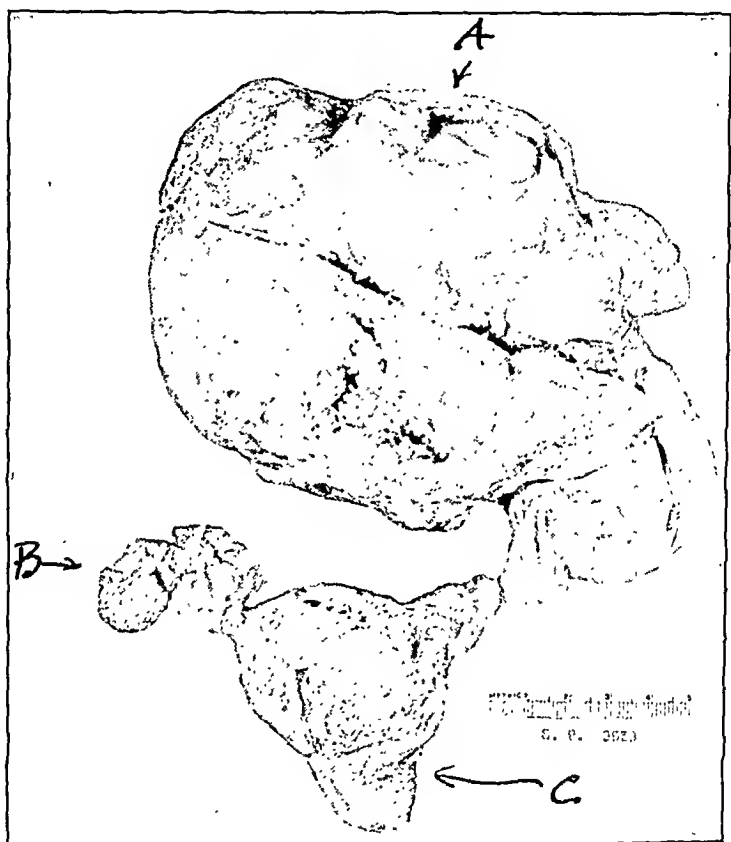


Fig. 1.—A, Tumor of left ovary; B, right tube and ovary; C, uterus.

Examination a few days later showed evidence of free fluid. Mass felt to right of midline coming up out of the pelvis extending to level of umbilicus, mobility restricted, not tender. On examination, uterus could not be differentiated from a large, hard, irregular nodular mass about the size of a five months' pregnancy. Mobility restricted but condition was not a frozen pelvis. Impression: Papillary cystadenocarcinoma of ovary. Laparotomy advised.

*Operation:* Anesthesia, nitrous oxide and ether. Midline lower abdominal incision. Large solid tumor mass with many papillary and cystic excrescences occupying the entire lower abdomen extending to level of umbilicus adherent to small intestines and omentum. All adhesions freed by blunt dissection and mass mobilized, when it was found to arise from the left ovary. On careful exploration no masses were found on the liver, omentum, intestines, or parietal peritoneum. The right tube and ovary were normal. Several small subperitoneal myomas on uterus. Mass extended posteriorly in back of the left broad ligament down to the level of the cervico-

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## PAPILLARY CYSTADENOCARCINOMA OF OVARY WITH HYDROTHORAX

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A CAREFUL search of the literature of the last twenty-five years has failed to disclose a single case similar to the one to be presented in this article. However, in 1937, Meigs and Cass<sup>1</sup> reported a series of seven cases of ovarian fibroma with ascites and hydrothorax, in which after removal of the tumor, the hydrothorax disappeared and the patient recovered.

Another article on the same subject was published<sup>2</sup> in November, 1937, by Rhoads and Terrell, who pointed out that because of the association of a pelvic tumor, apparently ovarian, with ascites and hydrothorax, a diagnosis of pelvic malignancy with chest metastases was made in several of these cases, as a result of which they were considered hopeless and operation was long deferred. Occasionally it may be impossible, Rhoads and Terrell state, even after partial aspiration, to exclude the presence of pulmonary metastases by x-ray, therefore they feel that an abdominal exploration in this type of case is justified and promises hope in a considerable number of cases in which the prognosis was previously regarded as hopeless.

Mrs. A. S., aged 50 (204382), was admitted to the service of Dr. B. M. Eis, on Aug. 9, 1937, complaining of heartburn and diarrhea. Family history irrelevant. Patient has been married 19 years, has one child 17 years old, has never been sick before. Menopause three years ago. For the last two months she has been complaining of heartburn, with gradually increasing dull epigastric pain until four days before admission, when a profuse, watery diarrhea began, persisting until admission. No other symptoms. On admission she had a temperature of 100.6° F., pulse 124, respirations 24, blood pressure 118/78. Flatness and markedly diminished breath sounds lower half of right chest. Heart normal. Abdomen: Fluid wave and shifting dullness. Mass felt in right lower quadrant arising from pelvis extending to level of umbilicus. Vaginal examination confirms impression that mass arises from pelvis. *Diagnosis*: Papillary cystadenocarcinoma of ovary with pulmonary metastases.

*Physical findings*: Kline test negative. Sedimentation: 62 mm. per hour. Blood count: Hg 62 per cent, white blood cells 7,850, polymorphonuclears 82 per cent, R.B.C., 3,050,000. Urine, acid; specific gravity 1.015; albumin, negative; sugar, negative; epithelial cells. Stool negative for occult blood. X-ray of chest: A homogeneous opacity involving the right chest indicating massive effusion.

the large abdominal lymphatic channels, and so retarding return of lymph through normal channels. We know that capillary permeability is affected by histamine and similar substances produced by tissue injury and degeneration, consequently it is a factor in the formation of lymphedema in a case such as ours, in which toxic substances formed in degenerated tumor tissue are being constantly absorbed. The possibility of capillary endothelial damage caused by anaphylactic reaction to degenerated tissue products must also be considered here. It is not inconceivable that the liver, in attempting to eliminate an excess of toxins, puts out an increased amount of lymph. The liver itself does not grossly become edematous because of its very liberal lymphatic drainage. Filtration, however, with respect to the primary capillaries at the other end of the portal system, is different. When the filtration pressure exceeds the oncotic pressure, plus endothelial damage, the division line between capillary filtration and reabsorption is shifted to the venous side, thereby resulting in increased venous pressure. Lymph so formed may be absorbed to some extent by the chyle vessels and be returned to lymphatic circulation with liver lymph. The greater quantity, however, is eliminated into the peritoneal and pleural cavities by the large serous surfaces of the viscera, omentum, peritoneal and pleural coats. Under normal conditions a balance of forces in serous cavities is essentially absorptive. Fluids and even particulate matter introduced are absorbed, the former by blood capillaries, the latter by lymph channels (Cunningham<sup>6</sup>). When the avenues of escape through blood capillaries and lymph channels are abrogated, as by toxic damage to endothelium, increased permeability based on anaphylaxis, obstruction to lymph, fluid becomes trapped in large serous cavities and a vicious cycle results in ascites, pleural effusion and, if allowed to go on, subcutaneous edema. The above possibilities, it is true, are speculative, but, we feel, present a physiologic explanation of the edema.

#### SUMMARY

A case of papillary cystadenocarcinoma of the ovary with hydrothorax is presented in which the effusion disappeared after removal of the tumor. It should be emphasized that a patient with an ovarian tumor and hydrothorax is entitled to abdominal exploration even though malignancy is suspected. The condition may be a benign ovarian fibroma, in which case the patient is cured; but even though the tumor be malignant, early removal may be followed by disappearance of the fluid and in some cases even by disappearance of metastases. This case is presented with a plea to the internist for thorough pelvic examination in every case of hydrothorax, and for operation whenever a pelvic tumor is found, even though malignancy is suspected.

We acknowledge with thanks the assistance of Dr. Victor Woronov in the preparation of this paper.

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uterine junction. A total hysterectomy and bilateral salpingo-oophorectomy were performed in the usual manner, raw surfaces peritonized with bladder reflection. Wound closed in layers without drainage (Fig. 1).

*Histologic Report:* Sheets of large polyhedral and cylindrical cells varying greatly in size, shape, and chromatin content of their nuclei, a number seen in a state of mitotic division. In places they tended to form acinar structures or appeared to be mounted on connective tissue stalks. Areas of necrosis were seen in places. The stroma was in places abundant, hyalinized, infiltrated with small round cells, large mononuclear cells and some polymorphonuclear leucocytes.

*Diagnosis:* Papillary cystadenocarcinoma of left ovary.

*Postoperative Course:* Patient ran a temperature from 100 to 102°, and on August 29 vaginal examination disclosed a bulging in the posterior cul-de-sac. The index finger was pushed through the vaginal vault and about 4 ounces of pus were evacuated. There was also a purulent discharge from the lower angle of the wound. Temperature thereafter remained normal.

X-ray of skull failed to reveal any evidence of metastasis. X-ray of chest revealed considerable improvement in the pathologic process, with evidence of residual thickened pleura at the right base. A diagnosis of metastatic disease of the ribs or lungs was not warranted from this study. Patient was discharged from the hospital on September 16. General condition good. Abdominal wound clean, granulating. Postoperative deep x-ray therapy given, a set of 20 high voltage treatments, abdomen and pelvis, 4,000 rat units. Patient has felt well since operation and examination on Jan. 17, 1938, showed a completely free, negative pelvis: wound firm, no free fluid, no masses, no tender areas. Chest negative. X-ray of the chest on January 13 showed no mediastinal, pulmonary or pleural pathology.

#### DISCUSSION

A point of unusual interest in this case is the x-ray picture after chest aspiration in which two shadows appear, described by the roentgenologist as either metastases or residual fluid. These shadows disappeared on the plate taken before the patient left the hospital, a period of only two weeks. If we accept the postulate that these shadows were metastases, it follows that they disappeared two weeks after removal of the primary tumor. This, however, occurs in the milder types of early malignant change, whereas in the case presented, the malignancy seems to be moderately advanced. Even the possibility of disappearance of metastatic foci in a case of this type emphasizes the importance of early operation. In view of the fact that roentgenologically the two chest shadows appearing after removal of the fluid were considered as either metastatic or residual fluid, the latter interpretation would tend to classify this case as belonging to the group reported by Meigs of ovarian fibroma with hydrothorax, the difference being that this patient had an ovarian cystadenocarcinoma instead of a fibroma. Meigs offers no explanation of the etiology of the hydrothorax in his cases. If we were to venture a physiologic hypothesis in explaining the coexistence of hydrothorax with ovarian tumors, we might consider the following:

It appears physiologically sound to state that more than one single factor is involved. Experimental work on animals, as described by Wiggers<sup>4</sup> in the reproduction of anasarca, indicates that the order of appearance is as follows: (1) elevation of venous pressure; (2) ascites; (3) hydrothorax; (4) subcutaneous and pulmonary edema. Edema is considered by some to be a compensatory mechanism through which an attempt is made to restore blood and fluids surrounding vital organs to a normal state. Aldrich<sup>5</sup> suggests that it may be protective, e.g., by diluting toxin. Wiggers tells us that forces and interactions in the production of edema are so many and variable that we must regard it as a chain of events in which an initial change leads to a series of subsequent alterations. In such a study, the serous cavities, it must be remembered, are considered part of the lymph drainage and productive system.

The initial factor in our case is the presence of a large pelvic tumor. This then presents the possibility of contributing to the chain of events by compression of

Biopsy specimens from several lesions were examined by Dr. A. C. Broders and diagnosed papillary adenocarcinoma Grade 1. On subsequent diagnostic curettement of the uterus no evidence of malignancy was found.

Five cases of primary adenocarcinoma of the vagina have been reported in the literature. Strachan described two cases, which represented an incidence of 0.55 per cent in 328 cases of gynecologic carcinoma. This is greater than in most similar series of cases. He likewise gives the incidence for all types of primary vaginal carcinoma as 3.9 per cent which is also relatively high.

Moench found two cases of primary adenocarcinoma in 59 primary vaginal malignancies in the Mayo Clinic material up to 1931. She states that one epithelioma of the vagina was found for every 43 epitheliomas of the cervix between the years 1915 and 1925.



Fig. 1.—Section of a gland of the Grade 1 adenocarcinoma situated beneath the squamous mucous membrane. This carcinoma is comparable in malignancy to the so-called malignant adenoma which not infrequently occurs in the large intestine.

Strachan quotes Gurlt who found 0.19 per cent of primary epitheliomas of the vagina in 59,600 collected cases. Other incidences of primary malignancies of the vagina, quoted by this author, ranged from 0.06 to 0.43 per cent. Strachan further states, "The percentage incidence of primary adenocarcinoma is therefore infinitesimal in any large series of gynecologic cancer, so that individual cases when they occur are usually reported."

Williams found only two undoubted cases of primary vaginal carcinoma in the records of the Pathological Department of Boston Hospital in twenty-five years. Neither was adenocarcinoma. With Moench's observation of only two instances of primary adenocarcinoma in 59 cases of primary carcinoma of the vagina, it is apparent that the incidence of primary adenocarcinoma of the vagina must be small indeed.

Emmert found 30 cases of primary carcinoma of the vagina in 1,546 cases of genital cancer in Barnard Free Skin and Cancer Hospital, St. Louis; none was adenocarcinoma. His study included seven additional cases from private practices. Of these, one case from Dr. Gellhorn's practice, a 27-year-old woman, was adenocarcinoma. There is no further description of this case.

# PRIMARY ADENOCARCINOMA OF THE VAGINA

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CARCINOMA of the vagina is uncommon. Most of those cases which occur are secondary to carcinoma elsewhere, usually higher in the genital or in the urinary tract. Of the small remaining group, the primary vaginal carcinomas, epitheliomas comprise by far the greater part; the rarest of all types is the primary adenocarcinoma.

The following case is one in which the diagnosis has been established microscopically, and the possibility of a primary growth from which the lesions might have metastasized appears to have been eliminated.

The patient is a white, 28-year-old, nulliparous female with this history: There had been a constant vaginal discharge from seven to eight years. This was usually worse after menstruation. In addition to the discharge, there was local irritation described by the patient as tingling and "sticking." During the past three years spotty bleeding had occurred at times, usually accompanied by an increase in the amount of discharge and the local irritation. Except for occasional mild dysmenorrhea, menstruation seemed normal. There was no history suggestive of pelvic inflammation or cystitis. A wide variety of treatment had been employed. Symptoms were almost invariably exaggerated. There were two exceptions to this: administration of estrogenic hormone and cervical cauterization to relieve a low-grade endocervicitis, were followed by some reduction in discharge and soreness. There were apparently spontaneous exacerbations and remissions at various times when the patient was under no treatment.

The patient presented a normal general appearance, temperature 98° F., pulse 72, blood pressure 116/76, height 65 inches, weight 125 pounds. Pupils round and equal reacting normally to light and accommodation. No exophthalmos or other apparent abnormality of the eyes. Teeth in good condition. Tongue clean and moist. Tonsils cleanly removed. No evidence of deformity, inflammation or other abnormality in the ears, nose, or throat. No cervical adenopathy. Thyroid not palpable and showing no evident enlargement. Tendon jerks present and normally active. No abnormal reflexes and a negative Romberg.

Chest showed good and equal expansion with normal breath sounds and resonance throughout. The heart sounds were regular and of normal quality; no evidence of cardiac enlargement. Fluoroscopy and flat films of the chest were negative. The breasts were well-developed, symmetrical, and were free from masses or tenderness.

The abdomen was nearly flat and without scars. There were no palpable masses; the liver was not palpable and was not percussibly enlarged. Kidneys and spleen were not palpable. No tenderness anywhere in the abdomen. No visible or palpable adenopathy in the inguinal regions.

The perineum presented the normal nulliparous appearance. There was no evidence of old or recent inflammation of the urethra, Cowper's or Bartholin's glands.

The cervix lay somewhat to the right of the midline. It had a normal appearance.

On examination of the vagina there were multiple, flat, hyperemic lesions varying in size from 0.1 cm. to 0.5 cm. in diameter. These were distributed throughout the entire vagina but were more numerous in the lower third.

On bimanual examination the uterus, including the slightly deviated cervix, was found movable, normal in size, shape, and position except as stated. There was no palpable pathology in the adnexa.

Urinalysis of a catheterized specimen showed no pus, blood, albumin, or sugar. Blood Kolmer and Kline were negative. Smears were negative for gram-negative diplococci and a saline suspension of the vaginal secretion showed no *Trichomonas vaginalis*.



## POSTENCEPHALITIC PARKINSONISM COMPLICATED BY PREGNANCY

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THE occurrence of pregnancy in patients with postencephalitic Parkinsonism is, according to some observers, a serious or even fatal complication. Roques<sup>1</sup> made a very extensive study, reviewed the literature up to 1928, and added a number of new cases. He concluded that pregnancy occurring during the acute stages of encephalitis apparently increases the chances of a resulting Parkinsonism and that in subsequent pregnancies this postencephalitic sequel becomes aggravated. Bland and Goldstein<sup>2</sup> hold the same ideas from their review of the literature and feel justified in concluding that this combination of conditions is not a happy one, the case they reported terminating fatally on the eighth day following delivery. Critchley,<sup>3</sup> who reported 7 cases, felt that pregnancy is not aggravating to Parkinsonism.

Roques reported 40 cases, Bland and Goldstein 1, Critchley 7, Tranquilli-Leali<sup>4</sup> 1, Voron, Pigeaud and Nova<sup>5</sup> 1, Ottow<sup>6</sup> 1, Achard<sup>7</sup> 4, De Rezendes 1, Thwaites Lastra, Bizzozero and Alegre<sup>8</sup> 1, and Hernández Ramirez<sup>10</sup> 1. We add to these, 2 patients with 3 pregnancies who have come under our observation at the Presbyterian Hospital.

CASE 1.—Mrs. E. Z. R., aged 20, was born in the United States. This patient was first seen in our out-patient obstetrical clinic on June 29, 1936. She had been amenorrheic since April 23, 1936. Her past history revealed that she had had diphtheria, and at the age of 10 she had fallen from a second floor porch. The tremors of the body were dated from the time of the fall. Menses began at 11, and had been recurring at regular (twenty-eight to thirty days) intervals, lasting three to four days with moderate flow. The patient had no history of infantile spasticity or rickets, having learned to walk at one year of age. She was 4 feet 11 inches tall and weighed 108 pounds. General physical examination was negative. Blood pressure was 110/80, hemoglobin 80 per cent, Wassermann reaction negative, vaginal smears negative, and urine normal. Pelvic measurements were within normal limits. Bimanual palpation revealed the presence of an early pregnancy. Because of the coarse generalized tremors, the patient was referred to the neurologic clinic.

Neurologic examination (Dr. J. Favill), July 1, 1936: No changes in the cranial nerves, coarse tremor of the tongue, and pupils that reacted normally to accommodation and light. There was a marked spasticity of both sides of the body, being more exaggerated on the left. There was little control of the left arm, the patient frequently calling the right into use to help the left carry out movements. The reflexes were all present but were slightly decreased on the left side. The speech was slow and tremulous with some slurring. The patient stated that the tremor was greatly exaggerated in the presence of strangers. A diagnosis of postencephalitic Parkinsonism was made, and a favorable prognosis given. Hyoscine hydrobromide, gr. 1/100 twice daily, was prescribed. This was changed to tincture stramonium, 30 drops three times daily, when it was found that the patient could not swallow tablets.

Combined neurologic and obstetric observation found the patient approaching term in an unchanged condition. She entered the hospital in labor at 1:00 P.M. on Jan. 1, 1937, having good contractions at three- to five-minute intervals. At 2:15 P.M. 4½ gr. of pentobarbital sodium and 1/200 gr. of hyoscine hydrobromide were administered and at 2:45 P.M. another 1½ gr. of pentobarbital were added. The patient was restless but cooperated well throughout labor. Dilatation proceeded, and

A review of the cases previously presented suggests that suspicion of primary vaginal adenocarcinoma might be occasioned only by the presence of one or more vaginal growths of considerable size. Such an appearance did not characterize the case presented. In this instance the gross appearance varied widely from the lesions previously described.

Our experience with this case would suggest that malignancy must be considered a possibility in any surface lesion of the vagina which is resistant to treatment.

Study of the group of cases makes it apparent that age is not an invariable factor and that pregnancy has nothing to do with the occurrence of this lesion.

*Differential Diagnosis.*—Differentiation of primary from secondary carcinoma presents some difficulty. Particularly the possibility of a primary lesion higher in the genital tract or urinary tract must be eliminated. Taussig has reported a case of hypernephroma in which the metastasis occurred near the external urethral opening. In addition to several other diagnostic points it was stated in this report that, "A primary malignancy at this point (perineurethral area) has practically never been observed." It is significant that in the case here presented a number of the lesions occurred within 2 to 3 cm. of the urethral opening.

*Treatment.*—Treatment in the cases previously reported has consisted of some surgical procedure combined with application of radium, or radium treatment alone. Surgery alone is regarded quite pessimistically by some authorities. The incidence of primary adenocarcinoma is too small to justify conclusions as to the most effective treatment. Electrocoagulation was employed in the present case, but too recently to make its effectiveness evident. Guarded prognosis appears to be eminently justifiable.

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Heuck and Hauser: Thirteen Cases of Malignant Chorionepithelioma, *Ztschr. f. Gynäk.* 117: 1, 1938.

A series of 13 cases of malignant chorionepitheliomas is reported. Five cases followed full-term labor or abortion, seven occurred after hydatid mole and one followed a tubal pregnancy. Cures were obtained in 50 per cent of the cases. The Aschheim-Zondek reaction proved of the utmost importance not only diagnostically but also to determine the results of treatment. Lutein cysts were found only in cases of hydatid mole (in 5 out of the 7 cases). If after removal of an hydatid mole, lutein cysts appear, it is a highly suspicious indication of chorionepithelioma but not absolute proof.

It is not possible to determine whether or not a chorionepithelioma is present from the microscopic examination of an hydatid mole; an Aschheim-Zondek test is most helpful.

Metastases were observed in six of the 13 cases and in five led to death.

cident. The patient nursed her baby and left the hospital on the tenth postpartum day. Follow-up neurologic examination revealed no change in the patient's condition.

### DISCUSSION

The apparently harmless effect of the pregnancies upon the Parkinsonism in these two patients leads us to feel that the authors who took such a serious view of the association of these conditions have been unduly alarming. This difference in opinion may be explained when we state that most of Roques' patients became pregnant soon after their attacks of acute epidemic encephalitis and the patient reported by Bland and Goldstein had the onset of her Parkinsonism three years before her pregnancy. The disease of the patients here reported was of long standing, 10 and 18 years, respectively. Roques states that pregnancy is contraindicated in patients with post-encephalitic Parkinsonism until at least four years have elapsed since the disease has become stationary. In recent cases he advises therapeutic abortion, and in all instances he stresses very close observation with termination of the pregnancy as soon as there are any signs of progress in the neurologic condition regardless of the stage of gestation. This appears to be sound advice but, as Roques himself says, he may have a rather distorted view of the situation because the cases he reviewed from the literature and those of his own were all patients in whom the acute encephalitis was fairly recent or in whom the Parkinsonism was aggravated by the pregnancy. On the other hand there may have been any number of patients with Parkinson's disease who may have weathered pregnancy, labor, the puerperium and the lactation period uneventfully, and were therefore considered not worthy of report.

According to other authors, the danger periods in pregnancy for these patients are the early months with the necessary bodily readjustments, the labor with its attendant stress and strain, the puerperium with the changes meant to bring the organism back toward a normal state and the lactation period with the constant strain upon the maternal mechanism.

In all reports studied the pregnancy and labor were not found to have been affected by the Parkinsonism, most authors feeling that labor is facilitated because the pain threshold in these patients is raised and the mental acumen lowered. Lower limb spasticity may present a difficulty in making the use of the lithotomy position rather impossible. Roques favors a short second stage with delivery as soon as conditions are favorable for low forceps application. All authors agree that the presence of Parkinsonism does not influence the incidence of sterility, abortion, or pregnancy toxemia.

After observing these two patients we feel that chronic postencephalitic Parkinsonism is no contraindication to pregnancy, and that the neurologic condition is not adversely affected by the pregnancy, puerperium, lactation, or even the labor, providing prolonged inhalation anesthesia is not employed. Under the combined care of the obstetrician and neurologist, and with proper mild sedation throughout the pregnancy, it is felt that the patient with chronic Parkinsonism is no worse an obstetric risk than is the normal woman. The only factor that may lead to restriction of activity for such patients is the individual ability to maintain equilibrium stability in the face of the increased weight and unwieldy abdominal protruberance occurring late in pregnancy. As one of our neurologic consultants put it, "the economic situation of the patient should be the guide as to the number of pregnancies she may have, and on this basis alone should sterilization become a consideration."

The only precaution that we advocate in these patients is one relating to anesthesia. All general inhalation anesthesia produces some cerebral edema. The addition of such edema to a brain which has already been insulted may prove to be annoying or even dangerous. This is clearly demonstrated in our two patients. Patient 1, in her first labor, had prolonged ethylene-oxygen analgesia and deep anesthesia for the episiotomy repair. She exhibited an unusual amount of post-delivery vomiting and restlessness in spite of adequate prepartum sedation. This was not seen after her second labor or in Patient 2 where no truly deep anesthesia was used. Because of this, we believe that in patients having postencephalitic Parkinsonism who come to the delivery table, an effort should be made to use anesthesia other than of the inhalation types. If these are not available, a minimum of inhalation anesthesia or better yet analgesia should be administered by an expert anesthetist.

at 4:50 P.M. the membranes were artificially ruptured. At 6:10 P.M. ethylene-oxygen analgesia was started and at 6:38 P.M., after episiotomy, the patient delivered a 6 pound 5½ ounce female child. The baby was somewhat apneic but was readily resuscitated by the use of tracheal catheter and hot and cold water baths. The placenta was expressed at 6:45 P.M. The episiotomy was repaired with the patient under gas anesthesia.

The patient was returned to the ward where she was found to be very restless and tossed about considerably, having several attacks of vomiting. The restlessness did not subside and became so pronounced that at 12:10 A.M. it was necessary to administer sedation in the form of a retention enema of sodium bromide and chloral hydrate. Following this she had an uneventful puerperium, nursed her baby, and left the hospital on the tenth post-partum day.

On follow-up examination in the neurologic clinic, July 21, 1937, the patient was found to be in an unchanged condition, the pregnancy having had no demonstrable effect upon the Parkinsonism.

The patient again appeared in the prenatal clinic on July 1, 1938 with the history of having had her last menstrual period on Jan. 24, 1938. During the first two months of this pregnancy there had been some nausea and vomiting, but since that time she had been well. She was found to be about six months pregnant, weighed 121¼ pounds, had a blood pressure of 122/68, a negative Wassermann, a hemoglobin of 80 per cent and a normal urine. The neurologic condition was the same as on discharge with the last pregnancy. The patient was followed to term with the only recommendation being that she have a hospital delivery. She was admitted to the hospital on Oct. 30, 1938 in labor. Labor began at 6:00 A.M. At 9:40 A.M. the membranes ruptured spontaneously and she delivered normally at 9:50 A.M. after episiotomy. The episiotomy was repaired very rapidly (ten minutes) under very light gas anesthesia. Neurologic examination during the puerperal period (Dr. L. Avery) revealed no change from the previous condition and elicited no special precautions as to nursing the baby or subsequent pregnancies.

CASE 2.—Mrs. P. H., aged 23, was born in the United States. She appeared in the out-patient department prenatal clinic as a primagravida, her last menstrual period having been on May 15, 1937, and her first examination took place on Jan. 10, 1938. She had been born at full term, developed normally and graduated from grade school at 14. The past history revealed an attack of influenza in childhood and a fall when 5 years of age. Following this fall she developed a tremor of the right side of the body and head. Menses began at 13, came irregularly at two- to three-month intervals, lasted four to five days and the flow was moderate. Physical examination revealed no abnormalities except as recorded in the neurologic clinic. The patient was 5 feet 2 inches tall and weighed 139¾ pounds. Laboratory tests revealed negative Wassermann reaction and vaginal smears, blood pressure 120/80, hemoglobin 80 per cent, and urine normal.

Neurologic examination (Dr. W. Haines), Jan. 10, 1938: "History of tremors since a fall at 5 years of age. Tremors more marked on right side, and can be controlled to some extent by effort on the part of the patient. No changes in the special senses. No changes in the cranial nerves, normal sensation, poor coordination, tremors of extremities and head more marked on the right side with the right hand held in a clawlike spastic manner and the head tremor resembling a torticollis." A diagnosis of postencephalitic Parkinsonism was made. No specific treatment was recommended except that hospital delivery was advised and prolonged inhalation anesthesia, especially with ether, was cautioned against.

The patient went into labor at 9:00 P.M. on Feb. 16, 1938 and entered the hospital at 1:00 A.M. on Feb. 17. Labor progressed satisfactorily and the patient delivered spontaneously, without episiotomy, at 4:36 A.M. The placenta was expressed at 4:41 A.M. The patient had a small amount of ethylene-oxygen analgesia, with no true anesthesia. She reacted in all ways as does the normal patient. The baby weighed 7 pounds 5 ounces, cried spontaneously and was normal in all respects. The puerperium was uneventful except for a slight temperature rise on the third and fourth postpartum days ascribed to subinvolution. Following the use of fluid extract of ergot, the uterus descended and the puerperium progressed without further in-

The patient had had amenorrhea associated with intermittent vaginal bleeding and occasional pain since her discharge from the hospital. The bleeding and pain had become more severe on October 21 and had persisted until she entered the hospital. The patient appeared markedly pale, weak, and complained of sharp lower abdominal pain. Again the chief finding on physical examination was a tender football-size mass filling the left lower abdomen and seemingly springing from the left side of the pelvis. The mass was distinctly more tender on this admission. The temperature was 102° F.; pulse, 105; respiration, 26; blood pressure 136/70. The admission blood count again revealed a normocytic anemia and leucocytosis: Hb, 50 per cent; red blood count, 2,620,000; white blood count, 37,600; polymorphonuclears, 94 per cent.

A blood transfusion was administered and an emergency laparotomy was performed on the evening of admission. A hemorrhagic foul-smelling, necrotic mass was found filling the left pelvis and extending into the left abdominal cavity, almost to the umbilicus. The right tube and ovary were normal; the uterine wall was intact. As the gangrenous mass was being removed, two small fetuses came into view. The left tube and ovary were not recognizable. The foul, hemorrhagic material was removed as completely as possible. A portion of the unorganized mass which was adherent to the mesentery of the sigmoid was not disturbed. The uterus was then removed. A drainage tube and gauze packing were inserted into the cul-de-sac.

The patient received four blood transfusions within ten days of operation, and responded excellently. Complete recovery was delayed by a subfascial collection of pus which was drained under anesthesia on Nov. 24, 1938. The patient was discharged in good condition on Dec. 11, 1938.

*Excerpts from Pathologic Report:* "Two small male fetuses measuring 4.5 and 4.0 cm. accompany the specimen" (an enlarged supravaginally amputated uterus).

"*Diagnosis:* (1) Twin ectopic pregnancy. (2) Suppurative perimetritis with diffuse myometritis."

*Remarks:* One cannot state absolutely whether this case of twin ectopic pregnancy was tubal or abdominal in origin. The fact that no left tube or ovary was seen macroscopically or microscopically seems to indicate that the pregnancy was primarily tubal and that stretching and inflammation of the tube caused localized vascular damage and gangrene with or without rupture. It is also impossible to state definitely whether the twins were monochorial or dichorial in origin since placental or chorionic tissue could not be found. The fetuses appeared to be about three or four months of age, more mature than the measurements indicated. They were well preserved and no abnormalities were evident.

CASE 2.—Y. B. (No. 9129), aged 28, a nullipara, entered the hospital with chief complaints of low cramplike abdominal pain and bleeding. She had been married eight years. Shortly after her marriage she was told by her family physician that she could not conceive because of a retroverted uterus. Menstruation had always been normal except for mild dysmenorrhea. Her last menstrual period was Sept. 20, 1938. On Nov. 19, 1938, the patient noticed vaginal bleeding. The bleeding was scanty and intermittent and her physician treated her for threatened abortion. On Dec. 1, 1938, the bleeding became more profuse and the patient felt severe knife-like pelvic pain. A consultant advised immediate hospitalization.

Physical examination revealed a young white female approximately 30 years of age, very pale and restless and in extreme distress from abdominal pain. The temperature was 100° F.; pulse, 110; respiration, 30; blood pressure, 120/70. The significant finding on physical examination was a rigid, tender abdomen. Pelvic examination revealed extreme tenderness in the right cul-de-sac with bulging.

The admission blood count showed a normocytic anemia with leucocytosis to be present: Hb, 56 per cent; red blood count, 2,700,000; white blood count, 18,000; polymorphonuclears, 80 per cent. The urinalysis was negative. A diagnosis of ectopic pregnancy was made.

On the evening of admission an emergency laparotomy was performed. The peritoneum was congested and purplish; free hemorrhagic fluid was present in the peritoneal cavity. The right tube was enlarged to the size of a large pear and ad-

## CONCLUSIONS

1. Chronic postencephalitic Parkinsonism is not a contraindication to pregnancy.
2. Mild sedation throughout pregnancy is advised.
3. These patients may nurse their babies.
4. Pregnancy, labor, and the puerperium are not affected by the presence of the Parkinson syndrome.
5. Precaution must be taken in using prolonged inhalation anesthesia on patients with Parkinsonism.

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310 SOUTH MICHIGAN AVENUE

## REPORT OF TWO CASES OF TWINNING IN ECTOPIC PREGNANCY

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AREY,<sup>1-3</sup> in 1923, discussed the embryology of unilateral twin ectopic pregnancies and reviewed all reported cases. He found what he considered 40 authentic, 8 questionable, and 4 doubtful presentations in the literature.

Falk and Blinick,<sup>5</sup> in November, 1937, recorded two cases of their own that occurred in Harlem Hospital in New York and reviewed all the additional cases on record since 1923. They accepted, as authentic, 65 cases. I have been unable to find any recorded cases since November, 1937. Two additional cases of unilateral twin ectopic pregnancies are now presented, both of which occurred in Mount Sinai Hospital, Philadelphia, within a period of five weeks.

CASE 1.—A. S. (No. 8506), aged 36 years, first entered the hospital July 25, 1938, with chief complaints of pain in the lower left quadrant, chills, and fever. The patient was a para v, gravida v, her last delivery occurring eight years ago. For the past five years the patient had not been living with her husband. Her menses were always normal. The last menstrual period was July 18.

Physical examination revealed an obese, pallid white female about 38 years of age who complained of weakness but did not appear to be in acute distress. Her temperature was 101.8° F.; pulse, 94; respiration, 30; blood pressure 120/70. A slightly tender mass was palpated in the left lower quadrant that seemed to arise from the pelvis and extend up to the umbilicus. Because of the unusual obesity, the pelvic examination was unsatisfactory. The cervix appeared normal. A normocytic anemia associated with leucocytosis was present: Hb, 62 per cent; red blood count, 3,140,000; white blood count, 19,000; polymorphonuclears, 83 per cent.

It was thought that the patient had a degenerating fibroma of the uterus. Medical consultants advised against a laparotomy. With conservative treatment the temperature dropped to normal in two days and the patient was discharged on August 10, with instructions to report later for operation.

Three months later, on Oct. 31, 1938, the patient was again admitted with vaginal bleeding and knifelike pain in the left lower quadrant, dating since Oct. 21, 1938.

On admission, the patient appeared to be an acutely ill, well-developed, pubescent girl. Her temperature was 100° F., and her pulse and respiratory rates were 120 and 20, respectively. The blood pressure was 96/52. General physical examination revealed marked pallor of the skin and mucous membranes, a hemic (functional) systolic murmur at the pulmonic area, a palpable spleen, a single ecchymosis on the anterior surface of the left thigh, and steady vaginal bleeding through a falciform hymen. Rectal examination of the pelvic organs revealed no abnormality. Jaundice, lymphadenopathy, and gingival hemorrhage were notably absent. Blood studies disclosed the presence of a severe normocytic anemia with 45 per cent of hemoglobin (Sahli), 2,350,000 erythrocytes, 18,700 leucocytes, and 7.2 per cent of reticulocytes. The fragility of the erythrocytes was normal. The bleeding and coagulation times were seven and four minutes, respectively, and the platelet count, 190,000. The blood sugar and urea nitrogen values were within normal limits, and the blood Wassermann reaction was negative. A specimen of urine obtained by catheterization showed no abnormal constituents. The basal metabolic rate was plus 7 per cent.

In the absence of laboratory findings pointing to the presence of a blood dyscrasia, a tentative diagnosis of dysfunctional uterine bleeding was made. The patient was given during the course of a week, in addition to a hypernutritious diet, three blood transfusions of 500 c.c. each, five daily intramuscular injections of anterior pituitary-like substance of 200 rat units each, and daily hypodermic injections of increasing doses of mocassin snake venom in 1:3,000 dilution. The initial dose of the latter was 0.4 c.c. and the maximum dose, reached in four days and maintained for three additional days, was 1.0 c.c. The uterine bleeding continued unabated, and the anemia persisted despite the multiple blood transfusions. Repeated blood studies showed a rising bleeding time (from seven to twelve minutes), a falling platelet count (from 190,000 to 100,000), and a total absence of clot retraction.

The presence of essential thrombocytopenic purpura was suspected in view of the altered hematologic findings. This diagnosis was further supported by the elimination of an organic uterine lesion through curettage (the endometrium was atrophic and dysplastic) and by the exclusion of defective hematopoiesis through study of aspirated, sternal bone marrow. On this basis, in addition to repeated blood transfusions, therapeutic agents of reputed value in essential thrombocytopenic purpura were tried, namely, large oral doses of cevitamic acid,<sup>5</sup> massive injections of calcium and parathormone,<sup>6</sup> and roentgen irradiation of the spleen.<sup>7</sup> A week of such intensive therapy was fruitless. On June 30, 1938, after fourteen days of hospitalization, the uterine bleeding was as severe as on admission and the patient's hemoglobin was 50 per cent (Sahli) despite the five transfusions. The splenic enlargement increased, and the hematologic picture of thrombocytopenic purpura became definite, namely, complete absence of clot retraction and reduction of the platelet count to 80,000. The failure of all modes of nonsurgical therapy, the continued uterine bleeding, and the presence of normal bone marrow seemed to warrant a splenectomy which was performed by Dr. B. Lipshutz on July 1, 1938. The operation was preceded and followed by blood transfusions. The patient suffered no unusual reaction.

The anticipated salutary effect of the splenectomy was prompt and dramatic. The previously refractory uterine bleeding ceased abruptly within twenty-four hours of the operation. The splenectomy wound healed by primary intention and the patient, afebrile and symptom-free, was discharged from the hospital on the tenth post-operative day. She menstruated normally five weeks after the splenectomy and at twenty-eight-day intervals to date. The patient has remained in good physical condition and gained 12 pounds during the past five months. On Dec. 20, 1938, her hemoglobin was 102 per cent (Sahli), the erythrocytes 5,270,000, and the platelet count 230,000.

#### COMMENT

Essential thrombocytopenic purpura may defy recognition when there is no numerical reduction of the circulating platelets. In such instances, study of the clot retraction and examination of the bone marrow may be valuable. The absence of clot retraction denotes a qualitative alteration of the platelets which renders them incapable of aiding clot formation. The absence from the bone marrow of megakaryo-

herent to the sigmoid posteriorly. While the tube was being delivered it ruptured and two small fetuses dropped into the pelvis. The tube was removed and the peritoneum was closed without drainage.

The patient had an uneventful recovery and was discharged on Jan. 14, 1939, in good condition.

*Excerpts from Pathologic Report:* "There are two small male fetuses measuring 5 cm. in length. These are well preserved and show no abnormalities. *Microscopic Diagnosis:* Ruptured tuboovarian pregnancy (probably primarily tubal)."

*Remarks.*—Although the cord attachments of the fetuses could not be made out, the cavity from which the fetuses dropped was easily discernible in the removed specimen. The cavity was lined by a bluish membrane and in one area there was a rounded mass of chorionic tissue about 4 cm. in diameter. This case appears to be an example of monochorial tubal twin pregnancy.

#### SUMMARY

Two cases of unilateral twin ectopic pregnancy are presented, bringing the total number of reported cases to 67. That both cases should have occurred in one hospital in a period of five weeks is a rare and interesting medical coincidence.

I wish to take this opportunity to thank Dr. Charles Mazer and Dr. Charles Wachsh for permitting me to report these cases.

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## SEVERE MENORRHAGIA AS THE ONLY SYMPTOM OF ESSENTIAL THROMBOCYTOPENIC PURPURA CURED BY SPLENECTOMY\*

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**D**YSFUNCTIONAL uterine bleeding occurs quite frequently during puberty. It is often of such severity as to require heroic treatment, and occasionally terminates fatally. The cause of such bleeding is generally attributed to the same type of endocrine derangement responsible for the dysfunctional menometrorrhagia of mature women. However, the occasional occurrence of fatal uterine hemorrhage in the course of a blood dyscrasia, such as leucemia,<sup>1</sup> pernicious anemia,<sup>2</sup> or thrombocytopenic purpura,<sup>3</sup> makes a thorough search for obscure hematologic factors imperative in every instance of excessive uterine bleeding during puberty. The recognition of so singular a cause of uterine hemorrhage, even though seldom, may be life-saving by enabling the application of specific therapy.<sup>4</sup> The basic importance of this principle is illustrated by the following case history which describes the occurrence of almost mortal menorrhagia as the only symptom of essential thrombocytopenic purpura in a girl at puberty, and the curative effect of splenectomy.

A. F. (Mt. Sinai Hosp. Chart No. A5559), white female, aged 13, was admitted to the gynecologic ward, June 17, 1938, for the treatment of severe menorrhagia of three weeks' duration. This was her second menstruation. The first, which occurred six months earlier, on Dec. 20, 1937, was a moderate flow for fifteen days. Close questioning concerning her past medical history elicited the information that suturing was required to control an excessive gingival hemorrhage following extraction of a tooth at the age of 11 and that the slightest trauma usually produced noticeable ecchymoses. The patient's family and social histories were irrelevant.

\*Presented at a meeting of the Obstetrical Society of Philadelphia, January 5, 1939.



## PREGNANCY FOLLOWING MODIFIED ESTES OVARIAN TRANSPOSITION AND CUFF OPERATION ON OVIDUCT\*

VISUALIZATION OF END RESULTS AT THE TIME OF ELECTIVE SECTION

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ESTES devised a procedure which provided for the conservation of the ovary in those cases which presented such extensive adnexal pathology that a complete hysterectomy ordinarily would have been indicated. This preservation of the ovary permits the continuance of the menstrual cycle, maintains normal hormonal balance and provides the possibility of pregnancy. The procedure first consisted of removing the diseased tubes, carefully preserving the ovarian circulation, resecting the ovaries and saving as much as possible of the healthy ovarian tissue. These resected ovaries were then transposed over the cornual area of the extirpated tubes. Pregnancy resulted in about 8 per cent of the cases. Estes later modified this procedure by making a stab wound through the interstitial portion of the uterus in order to keep patent an opening into the uterine cavity.

At Bellevue Hospital we have further modified this technique. We ream out the interstitial area of the uterus, thereby preserving a more or less permanent opening, and suture the resected ovary over this newly created ostium into the uterine cavity.

The following case report is presented for two reasons: First, pregnancy occurred after performing a modified Estes transposition of the ovary, and a cuff operation on the tube of the opposite side. Second, we were able to visualize the end results of the above operative procedure at the time of elective cesarean section.

Mrs. M. B., 28 years of age, married two years, was admitted to Bellevue Hospital on May 30, 1936. Her chief complaint was sterility. She had been endeavoring to become pregnant for two years without success. No contraceptives were ever used. Her husband was found to be virile. Menstruation was regular, of the 28-day type, duration five to seven days. Patient had dysmenorrhea throughout her period which was severe enough on the first day to compel her to stay in bed. At times it was necessary for her to remain in bed throughout her entire period. There was no leucorrhea. She complained of slight dyspareunia.

The general health of the patient was good. Physical examination was essentially negative. Pelvic examination revealed cervix clean, smooth and in the axis of the vagina. Fundus was retroverted, normal in size and fairly movable. There was a left adnexal mass about 2 by 4 cm. prolapsed in the cul-de-sac. The right ovary was prolapsed, not enlarged. Right tube was palpable, probably clubbed. A diagnosis was made of sterility due to chronic adnexal disease occluding the tubes, and retroversion of the uterus.

On June 1, 1936, a Rubin test was negative at 180 mm. of pressure. Patient was then referred for treatment to the Sterility Clinic where she was given a course of diathermy treatments. A Rubin test repeated at this time was again negative.

She was then readmitted to the hospital for operation, which was done on Sept. 10, 1936.

The uterus was of normal size and third degree retroverted. Left tube was transformed into a hydrosalpinx, the ampullary portion being 4 cm. in diameter at its widest portion. The fimbriae were closed. The isthmic portion was occluded and the remainder of the tube was thickened. The hydrosalpinx was markedly adherent

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cytes, the progenitors of circulating platelets, is indicative of faulty platelet formation and also bespeaks the futility of splenectomy. On the other hand, the presence of megakaryocytes in the bone marrow suggests that the dyscrasia is not caused by defective hematopoiesis but rather by the probable elaboration of a platelet-destroying substance, thrombocytopen<sup>s</sup> by the spleen, the removal of which may prove eminently beneficial. The enervating effect of splenectomy in essential thrombocytopenic purpura may also be foretold, as suggested by Peck and his associates,<sup>9</sup> and as illustrated in this instance, by the refractoriness of the bleeding to the administration of moccasin snake venom.

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2116 SPRUCE STREET

1820 SPRUCE STREET

#### DISCUSSION

DR. GEORGE W. OUTERBRIDGE.—I have recently seen a remarkably similar case. This patient was also a white girl, 14 years of age. She was admitted to the Abington Hospital on the ninth of March, 1938, with a history of her first period having begun three weeks before, and having continued with profuse bleeding in spite of medication and injections by the family physician. Her history showed she had always developed purpuric areas following slight bruising, and since the onset of the bleeding she had developed several of these areas. She did not bleed excessively following cuts but in early childhood she would often awake with blood on her lips. The blood count showed 49 per cent hemoglobin, 1,900,000 red cells, and 7,600 white blood cells, 28,000 platelets, 6 per cent reticulocytes. The coagulation and bleeding times were each two minutes. Rectal examination was negative. She was given three transfusions, after which the bleeding stopped promptly. Nine days after admission her hemoglobin was 85 per cent and the red blood cells 4,200,000. She was discharged with instructions to her physician.

The patient was readmitted on May 3, after staying home for six weeks. She reported that she had remained free of bleeding for one month, except that on awakening she noticed blood on the lips and brushing of the teeth caused hemorrhage from the gums. Two weeks before readmission slight vaginal bleeding began and continued for ten days after which, during the five days prior to admission, it was profuse. The blood count showed hemoglobin 62 per cent with 3,000,000 red cells, but only 4,000 platelets. The platelet count was repeated a day or two later and 7,000 were found. A splenectomy was done on the 16th of May by Dr. Duncan B. Pfeiffer, following which the platelet counts were taken daily and rapidly increased, at one time reaching 500,000. She was discharged on June 22, 1938.

Her menstrual periods have been regular since her operation, of three days' duration, with no excessive bleeding and no discomfort. She has no bruising of the skin and no bleeding of the gums or lips. She is active in school and indulges in all the common activities of a girl of her age. She has gained 16 pounds since leaving the hospital.

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755 PARK AVENUE

## INTERSTITIAL PREGNANCY FOLLOWING SALPINGECTOMY\*

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PREGNANCY in the interstitial portion of the Fallopian tube is a rather rare condition. Since 1893, when Traub and Lawson Tait performed the first operations for interstitial pregnancy, some 200 cases have been reported. Wynne<sup>1</sup> stated that, in his review of 3,982 cases of extrauterine pregnancy, there were 58 of the interstitial type, an incidence of less than 1.5 per cent.

Still more uncommon are cases in which the pregnancy occurs in the interstitial portion of the tube following salpingectomy. Richardson<sup>2</sup> and DiPalma<sup>3</sup> each report such a case.

The diagnosis, according to Ash<sup>4</sup> who reviewed the literature up to 1932, is seldom made prior to rupture, and more seldom is it made or even suspected preoperatively. Mathieu and Wilson<sup>5</sup> found that, of the cases reviewed by them, one-fifth were unruptured.

The case to be reported is one of unruptured interstitial pregnancy in the left cornu of the uterus, three years after a left salpingectomy had been performed for tubal pregnancy.

Mrs. F. P., aged 31 years, was first seen on Aug. 22, 1938, complaining of pain in the left side of the abdomen and vaginal bleeding. She stated that she was in her usual health until May, 1938, when she missed a menstrual period. The last period began on April 23, and was normal as to amount and duration. About June 16, she began to bleed and developed a dull aching pain in the lower left quadrant of the abdomen. The bleeding lasted about a week, and with its cessation the pain subsided. About July 11, the symptoms recurred and lasted seven days. She felt well except for occasional pain in the left side until August 17, when the bleeding recurred and the pain became constant and more severe.

Menses began at age of 13, regular, 28 days, lasting four to five days. The patient had been married 13 years, had 2 children living and well, and had not had any miscarriages. In November, 1935, she was operated upon for a left tubal pregnancy. The past history was rather eventful. She had the usual childhood diseases, an appendectomy in 1923, a cholecystectomy in 1928, erysipelas in 1932, and a left salpingectomy for a suspected tubal pregnancy in 1935. However, the gross and histologic examination did not substantiate this diagnosis.

The physical examination showed a fairly well-nourished young female who did not appear to be ill. The heart, lungs, blood pressure, temperature, pulse, and respiration were normal. The abdomen was marked by 3 operative scars and was soft throughout. There was considerable tenderness in the lower left quadrant. The vulva and vagina were negative. The uterus was normal in size and position, but its mobility was limited. There was a mass about the size of a lemon adjacent to the left cornu which seemed to arise from the uterus. The right adnexa were not palpable. The blood count showed 4.5 million R.B.C., 7,500 W.B.C., and 71 per cent polymorphonuclears, hemoglobin 72 per cent. Urinalysis was negative. The sedimentation rate was 23 mm. in sixty minutes. From these findings a provisional diagnosis of left cornual pregnancy was made and operation advised.

The patient was admitted to the Temple University Hospital on August 25, and on the next day a laparotomy was performed, excising the old left rectus scar. The peritoneum was incised and the pelvis explored. There was no free fluid in the

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to the ovary and bound down in the cul-de-sac by adhesions. The right tube was thicker than normal and its fimbriated extremity was occluded. The ovary with the tube was prolapsed and adherent to the uterus.

Through a suprapubic midline incision, the adhesions about the right tube and ovary were freed by blunt dissection and the ovary and the tube brought up into the wound. Adhesions about the fimbriae were freed. Air was injected and the tube found to be patent. The adhesions about the left tube and ovary were freed and the large hydrosalpinx was dissected free, and on insufflation found to be also occluded in its inner third and therefore could not readily be reconstructed. It was then excised and the bleeding points clamped and ligated. The interstitial portion of the left tube was then reamed out with our specially devised reamer until the uterine cavity was entered. About one-third of the left ovary was resected and the freshly cut surface was sutured over the newly created uterine ostium with the use of double 0 interrupted chromic sutures. The right tube was then cuffed according to our method and suspended from the left wall of the pelvis by the Poole technique. The uterus was held out of the pelvis by a one point suspension, using a double No. 2 chromic suture. The abdomen was closed in the usual manner.

The postoperative convalescence was uneventful and the patient was discharged on Sept. 23, 1936. She reported to me Sept. 25, 1937, stating that her last period was on Aug. 14, 1937. A diagnosis of pregnancy of about six weeks was made, expected date of confinement being May 21, 1938.

The patient was admitted to our Obstetrical Service on May 10, 1938, at term with infrequent pains and at this time, although her pelvic measurements were normal, there was a question as to whether she was to be allowed to deliver spontaneously or whether a cesarean section was to be performed.

It is my feeling that a woman who subjects herself to any operative procedure in order to become pregnant is entitled to every chance for a living child. After consultation it was decided to perform a classical section. This was done on the morning of May 11, 1938, and a female child weighing 6 pounds 4½ ounces was delivered from the L.O.T. position. Upon inspection of the uterus it was found that the musculature was extensively thinned out near the fundus, especially where the Estes transplantation had been done at the left cornu. Finger inspection of the uterine cavity in this region disclosed that there was a cone extending up into the left cornu. What at one time consisted of the ovary was firmly incorporated on the left cornu of the uterus. The right tube was normal and the fimbriated extremity, where reconstruction had been done, was free. There were some fine filamentary adhesions to the posterior surface of the uterus. The uterus was closed in layers in the usual manner. Estimated blood loss was 400 c.c.

Patient's convalescence was uneventful. Both the mother and infant left the hospital in good condition on May 28, 1938. The mother has been seen at frequent intervals since the operation and a pelvic examination reveals that the uterus is in good position and no adnexal pathology is palpable. Where heretofore patient had complained of dysmenorrhea, she states that menstruation is now normal and free of pain. The baby is progressively gaining in weight and is in good condition.

### CONCLUSIONS

It is my opinion that had this patient been allowed to go into labor, there might have been a disastrous result for both mother and infant due to the fact that the musculature of the fundus was markedly thinned out. It is difficult to decide whether the thinning out of the fundal uterine musculature in this particular case is due to the operative procedure or to an inherent condition of the uterine fundus. However, the decision to perform an elective cesarean section resulted in a most gratifying outcome and bears out the point which I wish to stress, that where a woman has been subjected to operative procedure for the cure of sterility and pregnancy ensues, an elective section is indicated in the interest of both mother and child.

## INTERSTITIAL PREGNANCY\*

### FIVE MONTHS' GESTATION, WITH AN OBSERVATION OF THE PHENOMENON OF RUPTURE AT THE TIME OF OPERATION

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THE diagnosis of this type of tubal pregnancy before rupture is most difficult to make. Unless one has this condition in mind together with its criteria, the diagnosis may not be clear even at the time of operation, particularly if rupture has not occurred.

T. K., 27 years old, colored, married nine years, had not been able to become pregnant. She last menstruated on March 4, 1938. There were no unusual symptoms aside from right lower quadrant aches which were worse at the time of her menstrual menses. She was first seen in the prenatal clinic of the Cook County Hospital on June 27, 1938 and no abnormal findings were detected at that time. On July 24, 1938, at 8 A.M., she experienced sharp cramplike pains that began five minutes after coitus. These pains were mostly in the right lower quadrant, but at noon their location shifted to the region of the navel, and later that day consisted of a dull pain and soreness in the epigastrium. The patient was admitted to the hospital at 2 A.M., on July 25, 1938, with a temperature of 100° F., pulse 120, of good quality, and respirations 24. The epigastric pains became more severe and she had some pain referred to both shoulders. The respirations soon became rapid (44 per minute), the breath sounds were diminished in the right lower portion of the thorax, and it hurt the patient to breathe deeply. One member of the resident staff thought that moist râles were present anteriorly. The abdomen was difficult to palpate due to muscular rigidity. There was a mass originating from the pelvis that reached the level of the navel but was mostly to the left of the midline. Fetal heart tones could be heard. Vaginal examination revealed a long rather narrow conical soft cervix. It was difficult to determine by bimanual palpation if the mass felt through the abdomen consisted of an intrauterine pregnancy that was deviated to the left, or whether the uterus, in view of a cervix being disproportionate in size to the entire mass, was separated from it. The red count was 3,850,000 late in the morning.

A diagnosis was deferred until the chest could be x-rayed. This was reported that afternoon to be negative. The condition of the patient was good; therefore, she was placed under close observation. However, when a repeated red cell count that evening showed a drop to 2,500,000, it was decided to open the abdomen. We felt certain that we were dealing with some form of ectopic pregnancy. A pre-operative diagnosis of interstitial pregnancy was made purely through the clinical impression gained by the elimination of other related possibilities. Palpatory findings gave the impression that the pregnancy was not in the endometrial cavity. Intrauterine pregnancy was not considered because the cervix did not appear to be proportionate in size to a uterus of five months' gestation. Tubal pregnancy was excluded because of the rarity of such advanced gestation in the tubes. Abdominal pregnancy was considered, therefore, to be the only other possibility, but was not favored because the mass appeared to be too closely identified with the uterus itself.

At operation there was a moderate amount of free blood in the peritoneal cavity. The pregnancy was in the left uterine cornu and was unruptured. The left round ligament was at a higher level than the right one, and inferior and lateral to the site that contained the fetal sac. The left tube, which was normal, emerged from the side and inferior to the left angle. There was a small perforation on the posterior aspect of the uterine horn from which the patient was bleeding. In attempting to elevate the uterus to place clamps on the broad ligament for its amputation, the contents of the left uterine cornu began to rupture. This phenomenon consisted of a slow expression of the fetus in its amniotic sac which began at the point of

\*Presented at a meeting of the Chicago Gynecological Society, December 16, 1938.

peritoneal cavity. Several dense peritoneal and omental adhesions were encountered, cut, and ligated. The right tube and ovary were normal. The left tube was missing. The uterus was normal in size and position and presented a firm, irregular mass in the region of the left cornu. This mass consisted of ovary, omentum, sigmoid, and urinary bladder, adherent to each other and to the left cornu of the uterus. Dissection of this mass to free the intestine and bladder without perforation was accomplished at the expense of the uterine serosa, leaving a raw surface about 3 cm. in diameter on the fundus. The bleeding which resulted and the probability of the re-formation of adhesions at this point prompted the performing of a supravaginal hysterectomy and a left oophorectomy. The abdomen was closed in layers without drainage.

The patient had an uneventful postoperative course and was discharged on Sept. 8, 1938.

On Aug. 31, 1938, the following report was received from the pathologist. "The specimen consists of a uterus and ovary. The former is amputated above the cervix. It measures 8 by 5.5 by 4.5 cm. The wall is thickened and fibrotic. The left cornu of the uterine cavity leads directly into a large cystic cavity in the uterine wall. This cavity measures 2.5 cm. in diameter. The wall is lined with placental tissue and the lumen contains an 18 mm. fetus. The ovary is cystic. The block is quite cellular, although there is no evidence of malignancy or a corpus luteum."

This case of interstitial pregnancy is reported, first, because of the rarity of the condition; second, because of the unusual circumstances surrounding this particular case; third, to re-emphasize the importance of history as a factor in the diagnosis of extrauterine pregnancy; and fourth, as a probable instance of intrauterine transmigration of the fertilized ovum.

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#### DISCUSSION

DR. HARRY A. DUNCAN.—Transmigration of that fertilized ovum from the right tube across the fundus into the left tube would seem established from this case. I had not previously been able to satisfy myself that a fertilized ovum could make this journey when it is so easy for it to slip out of the cervix. In this particular case, however, where the external opening of the left tube seems to have been sealed off, it seems that this must have occurred.

Dr. Forman was most fortunate in making the diagnosis early and giving the proper treatment. This was especially fortunate because the mortality in interstitial pregnancy is three times as great as in tubal pregnancy. An aid in making the diagnosis of interstitial pregnancy is the fact that it does not rupture so early as true tubal pregnancy. Many of the fine signs of an interstitial pregnancy, however, such as the elevation of the cornu, the fact that the fundus is pushed to the opposite side and that the tube appears to arise from the inferior surface of the mass, and the uterus is rotated because of the pull of the round ligament, are evident only after the abdomen has been opened.

DR. EDWARD A. SCHUMANN.—A problem of great interest is the mechanism and the frequency of external migration of the ovum. Many of the specimens in which this phenomenon is thought to have occurred present tightly sealed tubes or a completely closed amputated tube on the side from which the ovum is presumed to originate. Why is it not possible that the ovum springs from the ovary on the unaffected side, and after passing down the tube becomes implanted in the dilated uterine cornua on the opposite side?

DR. FORMAN (closing).—We probably would not have taken out this uterus under ordinary circumstances, but she started to bleed from the site where we had ripped off the uterine serosa. The hysterectomy was done only for that reason and not because we suspected that our preoperative diagnosis, cornual pregnancy, was still tenable.

# A NEGLECTED SIGN FOR ROENTGENOLOGIC DIAGNOSIS OF INTRA-ABDOMINAL DERMOID CYST

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IN THIS short communication I would like to direct attention to a roentgenologic sign which, if present, permits an instantaneous anatomic diagnosis of an intra-abdominal dermoid cyst, even in such cases where the bony or dental anlagen of the tumor are not fully developed or escaped recognition by the roentgenologist.

The radiogram, Fig. 1, was taken of a patient, aged 25 years. It was the preliminary flat film of an intravenous urographic study ordered for differential diagnosis between a right ureteral concretion and a chronic recurrent appendicitis. The patient gave a history of attacks of pain over the right lower quadrant, radiating upwards to the right upper quadrant and at times associated with nausea and belching. These attacks occurred during the last two years once every three to eight months. Menstrual periods were regular, every four weeks, associated with a rather severe dysmenorrhea.

The x-ray film (Fig. 1) reveals a group of pathologic calcifications over the right wing of the os sacrum which is easily identified as teeth and bony structures. In addition, a fine regular, perfectly rounded, ring shaped shadow, as though drawn by a compass, is clearly visualized. This structure occupies the midportion of the pelvic cavity, emerges into the greater pelvis, and includes the above described calcifications. Its diameter is 13 cm., the breadth of the wall 1 to 3 mm.; the translucency for the x-rays is definitely increased inside the tumor upon comparison with the surrounding soft structures. The observation of a tumor giving a translucency instead of a density, at first thought, may appear very confusing; it is a well-established fact that solid tumors or cysts filled with liquid will cast a "shadow of soft tissue density" without any visualization of a wall except for pathologic calcifications. Since the structural detail of an x-ray picture, i.e., the appearance of shadows and translucencies of different intensity, is a direct function of the density of the transilluminated material, the conclusion must be drawn that the composition of the contents of the pathologic mass is the deciding factor.

According to Henke-Lubarsch's Handbook,<sup>8</sup> the contents of a dermoid are made up of, besides hair, an oily or fatty material, of a butter or vaseline-like consistency, and composed of neutral fats, fatty acid crystals, epidermis, cellular detritus, sweat drops, and occasionally cholesterolin. The fatty portion has been found to be as high as 29.15 per cent. Since the density of fat is 533 (water 1000, blood 1027), a 30 per cent fat content in the cyst gives a very satisfactory explanation for a perceptible increase in its translucency on an x-ray film.

Following an analysis of 91 dermoids observed in 79 patients by Glass and Rosenthal,<sup>6</sup> hair and sebaceous material was found in 81, and sebaceous material alone in 6 specimens, giving a total of 95.5 per cent of cases where the roentgenologic sign of increased translucency could have been expected. Teeth were found in 18, bones in 13, teeth and bones in 8 specimens, giving a total of only 48.4 per cent of cases where the leading roentgenologic sign of the typical dental and bony shadows could have been expected. This survey shows that the "tumor of increased translucency," if looked for, should be observed twice as frequently as the shadows of teeth and bones in an abnormal location.

From the roentgenologic signs, a definite diagnosis of dermoid cyst of the ovary was made in our case and confirmed on operation. The specimen measured 12 by 8.5 by 10 cm., and was filled with a yellow greasy soft material mixed with hair. In one area, bone tissue and well-formed teeth were noted.

perforation. The process was rather slow and progressive and could not be checked, but when the fetal sac and placental remnants were separated and removed from the site of their implantation, the left uterine cornu had the appearance of a structure that had literally been exploded. The bleeding became profuse and the uterus was amputated supracervically. Transfusion of 600 c.c. of blood was started as the abdomen was being closed. The recovery was uneventful and the patient was discharged from the hospital fourteen days postoperatively.



Fig. 1.—Anterior view of uterus showing the left round ligament (A), at a higher level than that on the right side, (B), and where the uterus was amputated (C). To the right the fetus is shown enclosed in the amniotic sac.

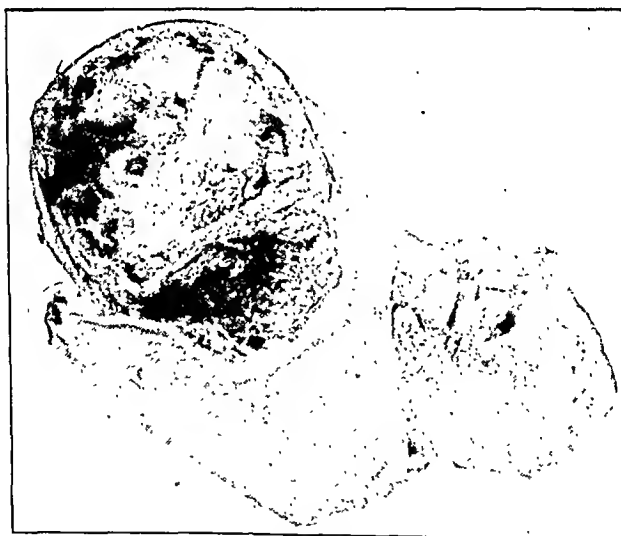


Fig. 2.—Posterior view of uterus showing the ruptured left uterine angle separated completely from the endometrial cavity (to the right).

The specimen consisted of the uterus in which the left broad ligament attachment was much longer than that of the right side. The appendages were therefore higher on that side. The cavity that contained the fetal sac was completely separated by a very thin septum from the uterine cavity. The fetus measured 16 cm. from head to rump.



lower of greater density. This phenomenon was explained as produced by "a layer of liquid fat floating on aqueous fluid within the tumor." On the picture it is noteworthy how little difference there is between the translucency of the liquid intracystic fat and the surrounding areated lung tissue.

While in small dermoids with a diameter well within the range of a gas-filled bowel loop, this may easily be overlooked or misinterpreted, tumors of middle or large size should demonstrate the above described sign. Counting 1 case of Laurell, 2 of Odquist, 1 of Aimé, 1 of Galifi, 1 of Heffernan, and the case here reported, 7 conclusive observations are at hand for further study. As already mentioned, in the absence of teeth and bony structures without visualization of a capsule, differential diagnosis from a lipoma has to be made. There is a unique radiogram on record (Brown<sup>2</sup>), revealing a large, highly translucent ring shadow produced by a gas filled ovarian cyst from perforation of a diverticulum of the sigmoid into the cyst cavity. On operation the sigmoid loop was firmly adherent to the cyst, and a "great deal of foul-smelling fluid and gas was found within the cyst." This very rare condition can easily be differentiated by its very strong transillumination from the moderate translucency of a dermoid cyst.

### SUMMARY

An intraperitoneal tumor which on a radiograph produces an increased translucency instead of a density is highly suggestive of a dermoid cyst. This becomes definite if the tumor wall itself is visualized. These findings will not be noted on an ordinary ovarian cyst or uterine fibroid. Differential diagnosis from lipoma and "gas filled ovarian cyst" is discussed.

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## SIMULTANEOUS EXTRA- AND INTRAUTERINE PREGNANCY

COMPLICATED BY ACUTE APPENDICITIS AND TUBAL RUPTURE,  
TERMINATING WITH A NORMAL INTRAUTERINE PREGNANCY

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COINCIDENT or combined extra- and intrauterine pregnancy is thought to have been first observed at autopsy by Duverney in 1708. Since this first observation numerous cases have appeared in the literature, but cases which terminated with a living baby have been exceedingly rare.

In their compilation of 217 cases, Gemmell and Murray find 81 cases which terminated with a living baby, or were progressing normally with the intrauterine pregnancy at the time the case was reported. Since this exhaustive compilation in 1932, Bell, Banister, Bondurant and Weintraub have reported cases. The case here reported brings the number to 86.

Upon careful study of the literature, no mention of this "ring shadow of increased translucency" in dermoid cysts was found among the numerous contributions in the last ten years on this subject. Two Swedish authors, Odquist<sup>14</sup> and Laurell,<sup>10</sup> observed this paradoxical sign and gave its correct interpretation. Among the three cases of Odquist, one presented a very diffuse limitation of the translucency without visualization of a capsule; on operation it was identified as a retroperitoneal lipoma.



Fig. 1.—Dermoid of the right ovary. *a*, Dental and bony anlagen. Arrows point to the visible cyst wall. Note the increased translucency inside the tumor caused by the high fat content of the dermoid cyst.

In the other contributions on the roentgenologic diagnosis of intraperitoneal dermoid cysts, the interest was exclusively focused upon the visualization of teeth and bones in the abdominal cavity, and the old observation of Odquist and Laurell was completely neglected. Looking through the pictures published so far, poor quality of the reproductions in several contributions prohibits statistical evaluation of this sign. In some of the published radiograms, the demarcation of the large round translucency is striking (Aimé,<sup>1</sup> Heffernan,<sup>7</sup> Galifi<sup>5</sup>), but this was not mentioned in the x-ray reports of these authors.

A very interesting observation was reported by Phemister, Steen and Volderauer<sup>15</sup> on an intrathoracic dermoid cyst. Within the large round tumor shadow, a horizontal level was noted separating an upper zone of greater translucency from a

pale and very faint. Diagnosis of ruptured ectopic pregnancy with hemorrhage was made and consent for surgery obtained. Patient went to surgery at 11:30 A.M., March 18, 1930.

The abdomen was opened in the midline, revealing an extensive intraperitoneal hemorrhage. Examination of the uterus revealed a clot adherent to the right tube one inch from the uterine horn. Removal of the clot revealed complete amputation of the tube at isthmus by the rupturing ectopic. Both ends at the amputation were bleeding freely. The distal portion of the right tube and the right ovary were distended with hemorrhagic infiltration. The left tube was edematous and adherent to the left ovary. The uterus was enlarged.

Surgical procedure consisted of right salpingo-ovaricectomy. Adhesions about the left ovary were liberated. Inspection of the cecum revealed a very acute appendix

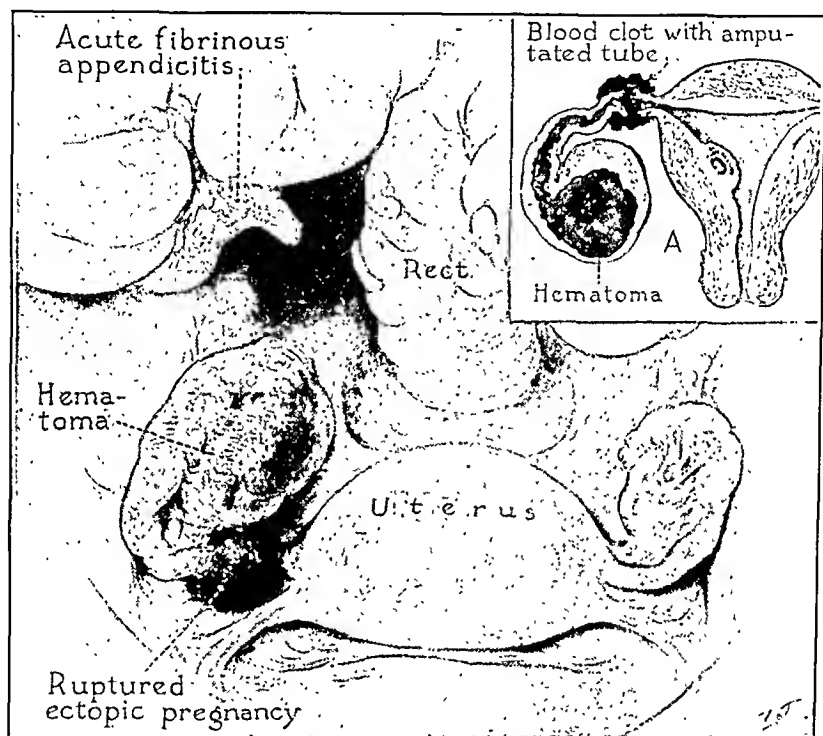


Fig. 1.—Illustration of the pathology as revealed upon intra-abdominal examination. *Insert A*: Diagrammatically showing extrauterine pregnancy in the isthmus of the right tube, complicating an intrauterine pregnancy. There was complete spontaneous amputation of the right tube at the isthmus by the expanding ectopic.

enveloped in its midportion by a thick, fibrinous exudate. The appendix was amputated and the ligated stump inverted with a purse-string suture of catgut. The abdomen was closed, with one large Penrose drain extending into the cul-de-sac.

Pathologic report: Hematosalpinx containing chorionic villi. Acute appendix.

Convalescence was extremely satisfactory. The temperature receded to 100° F. on the first postoperative day and became normal on the fourth. The patient was dismissed on the eleventh postoperative day.

The first postsurgical examination was made on April 25, four weeks after dismissal from the hospital. On pelvic examination, the uterus was about the size of an eight weeks' pregnancy. Diagnosis of intrauterine pregnancy was made and in retrospect a diagnosis of simultaneous intra- and extrauterine pregnancy. The patient positively stated that there had been no sex contact since her operation.

On Dec. 20, 1930 the patient was re-admitted to the hospital and delivered a normal female child weighing seven pounds and six ounces. The birth of the baby occurred just 277 days after her operation. Subsequently this patient had a second normal pregnancy, terminating with a healthy child. Her third pregnancy

As pointed out by Stein, an exact enumeration of cases of coincident or combined extra- and intrauterine pregnancy is exceedingly difficult because of the variety of captions under which they appear. Also, many cases have been reported with meager diagnostic and pathologic data so that there may be some doubt as to their eligibility. However, masterly efforts at compilation have been made by Zinke, Simpson, Neugebauer, Novak, Stein, and Gemmell and Murray and others. Zinke collected 88 cases in 1902 and Simpson 113 in 1904. The researches of Neugebauer raised the number to 244 in his second paper published in 1913. Novak, in 1926 adds 32 cases, including two of his own observation which had appeared in the literature subsequent to Neugebauer's compilation, making a total of 276 cases. Stein in 1928, without reference to Novak, adds 35 cases to Neugebauer's compilation, making a total of 279 cases. Stein's compilation includes 18 cases not found in Novak's which, added to Novak's, brings the total to 294 in 1928. By eliminating those cases not truly simultaneous as old ectopics complicating recent intrauterine pregnancy and other ineligible cases, Gemmell and Murray reduce the number to 217 cases. They reviewed the original report or an abstract of every case in the literature and their bibliography is apparently complete.

Novak finds 9 cases in which both extra- and intrauterine pregnancies went to term and both babies were delivered alive, the extrauterine by abdominal section. Bondurant and Weintraub report other cases, making 11 cases in which both intra- and extrauterine pregnancies produced a living baby. These 11 cases have been included in the above mentioned 86 cases terminating with a living baby.

#### CASE REPORT

Mrs. J. K., white, aged 21 years, was admitted to the Black Hills Methodist Hospital March 15, 1930 (Case No. 18042), with chief complaint of abdominal pain, very sharp, low in the abdomen, extending to the right side, and genital bleeding, since early morning. The pain continued with increasing severity until 12 M., when it was relieved for four hours by a hypodermic injection of morphine. At 4 P.M. the pain recurred with nausea and vomiting and continued with increasing severity until 8 P.M., when I saw the patient. She was admitted immediately to the hospital.

The patient had been married one year, had missed no periods, and no contraceptive methods were employed. Menstruation was normal, regular, twenty-eight-day type, four-days' duration, moderate flow and essentially painless. The patient had been exceptionally well until one month before, when she was shaken up in an automobile accident. Since the accident there had been a frequent appearance of a moderate genital bleeding. Five days before the bleeding became very profuse, accompanied by an acute abdominal pain. Both the pain and the bleeding quickly subsided and she felt very well until the onset of her present distress.

On examination the temperature was 99.4° F. by rectum, the pulse 80, good quality, the respiration 20. The abdomen was tender and slightly rigid on both sides below the navel, slightly more marked on the right side. Pelvic examination revealed the uterus enlarged above normal with definite softening of the cervix. The adnexa bilaterally were tender. There were no palpable masses but slight pressure upon the cervix elicited acute pain. Catheterized specimen of urine, turbid, light yellow, acid reaction, specific gravity 1.034, traces of albumin and acetone, occasional pus cell and few bacteria. Red blood cells 3,500,000, white 12,700. Provisional diagnosis, threatened abortion. One-fourth grain of codeine per hypodermic relieved the pain for several hours. A slight recurrence of pain the following day subsided without a sedative. Abdominal pain recurred March 17 at 9 P.M. Examination disclosed an increased tenderness in the right adnexa. The following morning at 4 A.M. pain became severe with nausea. Tenderness and rigidity had definitely localized over the cecal area. White cell count 15,700, red 3,100,000. Temperature 100° F. Diagnosis made of acute appendicitis complicating threatened abortion, and appendectomy advised. Surgery was declined. Ice bag, and ¼ gr. of codeine per hypodermic gave no relief. At 10 o'clock temperature rose to 102.2° F., pulse advanced to 110, and red cell count had decreased to 2,700,000. The patient was very

muscle fibers. Thus, from the microscopic picture, Dienst thought it appropriate to classify the altogether representative example of this group as capillary-hemangio-myxofibrosus-chorii.

Attention has been called to the presence of nucleated red blood cells within capillaries. Occasionally there has been noted endothelial proliferation with atypical cells and mitotic figures. Placental villi adjacent to chorioangioma reveal compression, and also degenerative changes; other neighboring villi may show increased number of ectatic capillaries in the stroma.

In its growth, the typical chorioangioma follows a benign course. Slight risk is involved for the mother unless the tumor reaches such size as to cause a mechanical obstructive dystocia. Vaginal bleeding is rarely an associated symptom. Chorioangiomas of large size, however, because of their frequent accompaniment with hydramnios and premature delivery, carry an increased fetal mortality that has been estimated between 30 and 40 per cent.

Mrs. R. K., a white, American housewife, 32 years of age, gravida ii, was admitted in labor to the Maternity Division of the Buffalo Children's Hospital on June 4, 1938. Abdominal examination disclosed a right occipitoanterior presentation and position; by rectal examination the cervix was felt to be half dilated.

Two hours following admission the membranes were ruptured artificially; a live normal male infant weighing 7 pounds 14 ounces was delivered spontaneously. The placenta and membranes were expelled completely following a modified Credé technique. Post-partum bleeding was estimated to be of normal amount. The puerperium was uneventful; the mother and child were discharged in good condition on June 16, 1938.

#### DESCRIPTION OF PLACENTA AND TUMOR

*Macroscopic.*—The placenta was discoid in shape. It measured 21 cm. in diameter and weighed 600 gm. The umbilical cord was inserted eccentrically 4 cm. from the margin. Situated on the fetal side of the placenta near the free margin was a hen's egg-sized mass measuring 9 by 6 by 4 cm., which caused a distinct elevation of the amnion. A thin layer of compressed chorionic villi measuring 0.2 cm. in width separated the tumor from the maternal surface. The tumor was well defined and could be easily shelled out from the surrounding tissues. Longitudinal section through the placenta revealed that the tumor was solid and firm. Toward the inner border was a hiluslike indentation into which placental tissue extended. Large blood vessels made their entry especially at the periphery of the tumor; fibrous tissue septa divided the tumor into lobules.

*Microscopic.*—The epithelium of the amnion covering the tumor was not well preserved. Between the amniotic surface and the margin of the tumor was a layer of loose connective tissue with cells showing elongated, dark-staining nuclei, and scattered cells with clear cytoplasm. The line of demarcation between the fibrous layer described and the tumor itself was regular and distinct. The tumor was composed of a sparse amount of connective tissue stroma and an abundance of capillary-sized spaces. These spaces were lined by endothelial cells which contained dark, spindle-shaped nuclei. In addition to these typical endothelial cells there was noted an occasional dark atypical cell; mitotic figures were not found. Many spaces were empty; others contained red blood cells. In still other spaces remnants of hemolyzed red blood cells were seen. A rare cell having the appearance of a nucleated red blood cell was observed. By special stain, the fibers in the stroma were shown to be chiefly collagenous and reticular. The pattern between the stroma and the spaces followed that of an angiomatous tumor. Scattered in the stroma were large cells with round, oval, or lobulated, usually eccentric nuclei, and with abundant, pink staining, sometimes foamy cytoplasm. By sudan stain yellow granules were demonstrated in the cytoplasm. In the indentations noted grossly lay placental tissue which showed ectasia of capillaries, necrosis, and focal calcification. Here amniotic epithelium was occasionally noted and the chorion was preserved.

In the hematoxylin and eosin stain, but especially in Van Gieson, Mallory, and modified Bielchowsky methods it was seen that the tumor was divided into lobules by

terminated in abortion and the fourth was complicated by a left salpingitis for which she was operated upon by another surgeon, and this pregnancy also terminated in abortion at the fourth month.

### SUMMARY

Using the compilation of Gemmell and Murray, the case reported is the eighty-sixth case of combined intra- and extrauterine pregnancy which terminated with a living baby. The complicating pathology which clouded the clinical picture enhances this rarity. The case was first diagnosed as pregnancy with threatened abortion. An acute appendix was next diagnosed as complicating a threatened abortion. Symptoms of concealed hemorrhage compelled a diagnosis of ruptured ectopic pregnancy. A complete spontaneous amputation of the right tube at the isthmus was found at operation. There was a complicating acute, fibrinous appendicitis. Pathologic examination demonstrated chorionic villi in the hematosalpinx. Diagnosis of intrauterine pregnancy was confirmed four weeks postsurgical by pelvic examination. The patient delivered a normal, female baby, weighing 7 pounds and 6 ounces, 277 days postsurgical. At present writing the product of this conception is a healthy, normal child.

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## CHORIOANGIOMA OF THE PLACENTA

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**W**E WISH to describe the gross and histologic findings in a case of a chorioangioma of the placenta.

While tumors arising from the epithelial elements of the placenta, such as hydatiform mole, choriadenoma, and chorionepithelioma are not uncommon, that neoplasm which apparently takes origin in the stroma of the chorionic villus, so-called chorioangioma, is of relatively infrequent occurrence. The first example of chorioangioma was described by John Clark in 1798. Up to 1924, Siddall collected 131 authenticated cases from the entire literature. In the past fourteen years, four additional reports have appeared in American journals.

Chorioangioma usually appears within the placenta as an elevation on the fetal side just beneath the amnion. Occasionally the tumor is pedunculated. The number may range from one to six; the size, from a millet seed to that of a child's head. Grossly, chorioangioma is a well-defined, solid tumor readily enucleated from the surrounding placental tissue, which is compressed to form a pseudocapsule. Regressive changes within the tumor itself including hemorrhage, pseudocyst formation, and calcification are known to develop. Thin septa often traverse the cut surface and produce a lobulated appearance. Blood vessels, after entrance into the tumor, run with the septa. Histologically, tumors demonstrate varying combinations of the following elements; blood vessels, fibrous, and myxomatous tissue, and, even, smooth

## ENDOMETRIOMA OF LAPAROTOMY SCARS

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THIS case is presented to show the entire life history of an abdominal wall endometrioma, with a suggested method of prevention.

Endometrial tumors usually follow laparotomy involving uterine operations and in my opinion are due to faulty technique. Frequently an assistant clamps several of the bleeding uterine sinuses and instead of discarding the forceps used, will, later, when closing the abdominal wall, grasp the peritoneum or fascia with the identical instruments, thereby implanting endometrial tissue. This is what happened in my case when an inexperienced assistant committed this error in technique.

The easiest way to avoid this accident is to insist on using fresh clean abdominal pads and fresh unused sterile instruments and needles for the wound closure, and the surgeon and assistants should change their gloves. If the abdominal wound margins (before opening the uterus), were well protected (pads), and if the operator and assistants make a complete change of gloves, fresh instruments including needles and towels, then, abdominal wall endometrioma will indeed become a rarity.

*Case Report.*—A white female aged 34 years was delivered Sept. 4, 1930 by cesarean section. At 16 years of age she suffered a fall resulting in a fracture of her coccyx and sacrum which healed at such an angle that the head could not pass. After 12 years of married life she became pregnant.

On her nineteenth day, a small bleb exuding serum at the lowest angle and an indurated area near the upper third of the healed wound were noted but thought to be due to probable extrusion of catgut, which did not occur.

On the twenty-third day two small sinuses were present; the one nearest the center of wound had opened and was discharging clear serum and the induration had practically disappeared. Her vaginal flow was reddish and the color continued until the end of her thirty-sixth day. Only two tiny granulating areas remained on the fortieth day.

When the patient was again seen six months later, I found a pea-sized hard movable nodule in the midline corresponding to the sinus following operation. Removal was advised but the patient decided to wait.

Eight months following operation the patient came in and stated that "her irregular movable lump got sore and swelled up at menstrual time," but again she put off operation. A diagnosis of endometrioma was made.

Nine months after operation she again came in with a lemon-sized growth in the fat and down to fascia. The tumor had increased markedly in size in the last four months. It was plum colored and always became "very sore" at the menstrual periods. Operation again postponed.

Finally June 14, 1933, slightly more than two years and nine months following her cesarean operation, I performed an elliptical excision, including the umbilicus, followed by a vertical fascial overlapping and wound closure. A piece of omentum attached to overlying scar was removed intact. Uterus was normal and entire abdomen free of adhesions.

*Pathologic Report* (Dr. S. H. Gray).—A mass (lemon-sized) extended from just beneath the epithelium down almost to the rectus sheath; the mass was stony hard and of a brownish gray color, traversed by pale yellowish strands. Several dark blue cysts less than 1 mm. and a number of somewhat larger brownish gray cysts were seen. The mass did not appear to rise from the skin and the skin was somewhat movable over the mass. It was adherent at a single point to the rectus sheath which points through the abdominal wall to meet it.

*Microscopic Findings.*—From the deeper layers of the corium down to the peritoneum there were scattered areas of endometrial tissue containing many endometrial glands. Some of these glands were cystic and contained old blood. No endometrial tissue was found in the omentum adherent to the old scar.

At present time, January 1, 1939, this patient is in perfect health.

bands or trabeculae of somewhat compressed, chiefly collagenous connective tissue. Many fibers in the stroma of the tumor were in connection with these trabeculae. Some trabeculae contained blood vessels which had moderately thick walls. There were also found necrotic villi, villi with ectatic capillaries, and areas of focal calcification.



Fig. 1.

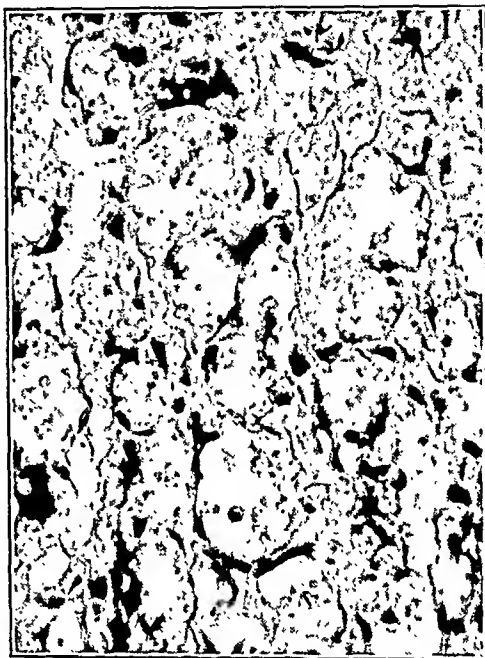


Fig. 2.

Fig. 1.—Placenta and tumor viewed from fetal surface.

Fig. 2.—Photomicrograph showing angiomatous structure of tumor.

Between the tumor proper and the placenta was a zone of compact fibrous tissue which contained large blood vessels. Here and immediately external to this zone were vessels showing thrombosis and calcification. The villi just adjacent to the tumor were compressed, and many showed regressive changes with organization of the stroma. Other villi showed an increased number of dilated capillaries. The intervillous spaces were narrowed and obliterated.

We are indebted to Dr. Kornel Terplan for his criticism and to Dr. Samuel Sanes for his assistance in preparation of this report.

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monia ratios were plotted against rate of flow, a well-defined curved zone was obtained. The nephrosis ratios were over 100 per cent; in the chart they fell outside of the normal zone.

### METHODS

The eclamptic subjects were patients having antepartum convulsions at term. They all had marked elevation of blood pressure, all had albuminuria and, with one exception, had pitting edema. The normal subjects were free of pitting edema and had no more than a trace of albumin in their urine; they also had no abnormal elevation of blood pressure.

Catheterized specimens of urine were obtained for the period, midnight to 6 A.M. Urinary acids and bases were determined by the methods of a previous publication.<sup>1</sup> The ammonia ratio was calculated from the equation:

$$R = \frac{NH_3}{(Cl + Po_4 + SO_4 + \text{organic acid}) - \text{fixed base}}$$

all expressed in M. Eq. per 100 c.c. urine. Rate of flow was calculated as cubic centimeters per kilo per hour. They are given in order that comparison may be made with the chart of the previous publication.

### RESULTS AND DISCUSSION

It will be observed in Table I that the ratios for eclampsia are higher than those for normal pregnancy. Four out of five of the ratios for normal pregnancy are below 90 per cent; results such as were obtained previously for normal controls. Seven out of 9 of the antepartum specimens from eclamptic patients gave ratios over 100 per cent. Ratios above 100 per cent were previously observed in nephrosis. Such high ratios were interpreted to mean that the renal epithelium, because of a state of irritation, neutralized part of the weak organic acid as well as all of the strong acid. There is again, therefore, the suggestion of excessive tubular activity: excessive re-sorption of water and sodium salts as a contributory cause of scanty urine and edema.

The ratios obtained post partum were normal, and elevated flow rates indicate the onset of diuresis. Here there is the suggestion of a receding state of irritation.

Some comment should be made on the ammonia coefficients ( $NH_3$ /total N) observed by Williams in toxemias. With pernicious vomiting, the ratios were consistently high and in eclampsia they were frequently somewhat elevated.<sup>3</sup> To interpret these ratios it must be borne in mind that ammonia production varies directly with excess acid in the urine. With total nitrogen output constant, these ratios also vary with excess acid. Consequently, with a starvation ketosis such as develops with pernicious vomiting these ratios tend to be high. Observations have been made on one such patient. The ratio of  $NH_3$ /total N was over 30 per cent compared to a normal of about 5 per cent; the ratio of  $NH_3$ /excess acid was 115 per cent compared to a normal of about 100 per cent. The ammonia production in this case of pernicious vomiting was therefore such as we have frequently observed for eclampsia and nephrosis; and the renal pathology of pernicious vomiting is likewise similar to that of nephrosis and eclampsia.

## THE EDEMA OF ECLAMPSIA

A. P. BRIGGS, M.D., AND RICHARD TORPIN, M.D., AUGUSTA, GA.

(From The Departments of Internal Medicine, Biochemistry, Obstetrics, and Gynecology)

**A**N INCREASING amount of interest attaches to renal factors which may be concerned with the clinical features of eclampsia. The edema is of special interest because patients developing eclampsia are usually those who gain weight to an abnormal degree during pregnancy.

The renal pathology of eclampsia resembles that of nephrosis, and the edema of eclampsia like that of nephrosis has been attributed to the depletion of plasma protein from albuminuria.

Recently, another renal factor has been suggested as a possible contributory cause for edema in nephrosis.<sup>1</sup> It was suggested that the so-called degenerated epithelium of the convoluted tubules may be in a state of irritation and actually the site of excessive functional activity. An excessive capacity for secretion of ammonia into the urine was observed to be characteristic of nephrosis, and excessive resorption of water and sodium salts from the glomerular filtrate was thought to be a factor tending to aggravate the edema.

The present study deals with the activity of ammonia production in the special type of "degenerative" nephritis which is associated with eclampsia.

For details of the development of theory in the correlation of ammonia production with functional activity of the kidneys reference should be made to previous publications.<sup>1, 2</sup> It will suffice to indicate that a critical study of the ammonia mechanism has revealed that it fails to perform consistently in any manner which, according to conventional teaching, would tend to maintain body neutrality or to regulate the fixed base composition of the body fluids. Ammonia production is, however, constantly related to excess of strong acid over fixed base in the urine. For this reason it has been assumed that production of ammonia by the renal epithelium is a local protective mechanism which is stimulated by and tends to neutralize the acid fluid formed within the tubules by the resorption of sodium bicarbonate from the glomerular filtrate. This stimulus response conception led to the study of the ratio of ammonia to excess acid in the urine as an expression of functional activity of the renal epithelium, first in normal individuals, and then in different types of nephritis. It was observed that the excess acid was rather completely neutralized in concentrated urines of the normal controls; with active diuresis the neutralization was much less complete, presumably because of less intimate contact between acid and epithelium. And when the am-

Most types of edema can be readily explained on a basis of a disturbance to the equilibrium between capillary blood pressure and the osmotic pressure of the plasma proteins. In eclampsia there is usually an increased venous pressure as well as a reduction of serum albumin;<sup>4</sup> each of these factors tends to produce edema. The female organism is, however, susceptible to fluctuations of water balance which are not so readily explained. At menstrual periods there is usually a definite increase in weight, presumably due to retention of water.<sup>5</sup> This possibly may be due to some influence of the pituitary on the renal epithelium leading to excessive resorption of fluid from the glomerular filtrate. In normal pregnancy there is a curious dilution of plasma electrolytes as well as of plasma protein.<sup>6</sup> This circumstance cannot be explained by any of the factors ordinarily considered, for none of them would tend to dilute the plasma electrolytes. Again there is the suggestion of distorted tubular resorption, possibly on an endocrine basis. In eclampsia there is a more definite expression of distorted tubule function in the excessive production of ammonia; an associated abnormality of tubular resorption is quite conceivable.

Of special interest is the question of an etiologic relation between the eclamptic convulsions and edema of the brain. It is realized that no close parallel holds between convulsions and subcutaneous edema, and that occasionally eclampsia occurs without visible edema. One of the patients of this series, L. S., had no edema, slight albuminuria, and total plasma protein was 6.4 gm. per cent; still she had antepartum convulsions associated with a rising blood pressure. We thought this was a case of eclampsia without edema. She had a normal puerperium.

Some light on the problem may be obtained by examination of other similar symptom complexes which are also associated with cerebral edema. In various types of anoxia, cerebral edema develops because of increased capillary permeability.<sup>7</sup> And the stimulation of brain centers in anoxia depends on the rate of development as well as the extent.<sup>8</sup> So a cerebral edema of small magnitude but developing abruptly might cause violent symptoms. Such a situation not infrequently occurs in acute nephritis where convulsions are associated with only slight nonpitting edema.

That an abrupt disturbance to the water balance does occur with convulsions in eclampsia is indicated by the work of Dieckmann,<sup>9</sup> who observed a decrease in blood volume and an increase in blood proteins to occur with the attacks. These findings indicate a change in capillary permeability with forcing out of plasma fluid into the previously well-filled extracellular spaces.

It seems most likely that the convulsions are precipitated by this factor which Dieckmann has discovered. But since the attacks occur most frequently in pregnancies with considerable edema, the factors of increased venous pressure, hypoproteinemia, and abnormal tubular resorption, must predispose by distention of tissue spaces.

Certain therapeutic implications appear to follow from the foregoing: sodium salts are restricted generally in any condition asso-

TABLE I. AMMONIA RATIOS IN ECLAMPSIA AND NORMAL PREGNANCY\*

SUBJECT	CHLORIDE	SULFATE	PHOS- PHATE	STRONG ORGANIC ACID	FIXED BASE	EXCESS ACID	AMMONIA	RATIO %	RATE OF FLOW	COMMENTS
Ingl	9.64	3.55	1.23	2.08	11.28	5.22	5.63	108	0.94	Ante-partum specimen
Clara	2.12	8.38	3.33	9.19	17.50	5.52	6.52	118	0.35	Ante-partum specimen
Nan C.	1.92	2.14	0.54	3.20	5.68	2.12	2.27	108	0.66	Ante-partum specimen
Scott	14.08	6.16	0.77	9.14	26.78	3.37	3.78	112	0.45	Ante-partum specimen
Cotter	8.32	5.48	0.85	11.36	14.90	11.11	10.50	94	0.85	Ante-partum specimen
Lewis	5.01	3.72	2.49	4.21	6.05	9.38	7.95	85	1.15	Ante-partum specimen
Price	10.40	7.12	1.60	7.91	17.08	9.95	12.94	130	0.20	Ante-partum specimen
Ruth H.	2.12	1.59	1.76	1.88	3.94	3.41	3.54	104	0.60	Ante-partum specimen
White	0.96	5.25	1.22	2.80	7.14	3.09	3.74	121	0.29	Ante-partum specimen
Cozy C.	3.85	3.02	0.64	1.15	5.34	3.32	2.02	61	1.55	Second day post partum
D. But.	11.62	8.07	1.25	3.54	17.48	7.00	4.84	69	1.35	First day post partum
Cora W.	15.02	8.47	1.40	4.41	22.63	6.67	6.34	95	1.01	First day post partum
Smith	2.92	2.24	0.81	1.22	6.36	0.83	0.73	88	0.41	First day, no edema
Summ.	3.28	3.18	2.29	4.56	4.97	8.34	7.44	89	0.65	Normal pregnancy
Clark	10.60	2.04	2.22	2.52	14.20	3.18	2.72	85	1.40	Normal pregnancy
Keen	12.36	1.65	1.74	2.74	14.00	4.49	4.15	93	0.59	Normal pregnancy
Nabon	5.76	0.54	0.95	1.61	7.40	1.46	1.03	71	1.12	Normal pregnancy
Spears	21.60	1.25	1.27	3.73	25.56	2.29	2.01	88	1.00	Normal pregnancy

\*Acids and bases expressed as M. Eq. per 100 c.c.

# Society Transactions

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## NEW YORK OBSTETRICAL SOCIETY

*MEETING OF DECEMBER 13, 1938*

The following papers were presented:

**Report of a Case of Ovarian Teratoma.** Dr. Thos. C. Peightal.

**The Treatment of Dysmenorrhea With Testosterone Propionate.** Drs. U. J. Salmon (by invitation), S. H. Geist, and R. I. Walter (by invitation). (For original article, see page 264.)

*MEETING OF JANUARY 10, 1939*

The following papers were presented:

**Toxemia of Pregnancy.** Dr. Maurice B. Strauss, Boston (by invitation). (For original article, see page 199.)

**Extraperitoneal Cesarean Section, With the Presentation of a New Technique.** (Moving picture demonstration.) Dr. Edward G. Waters.

*MEETING OF FEBRUARY 14, 1939*

The following papers were presented:

**Pregnancy Following Modified Estes Ovarian Transposition and Cuff Operation on Oviduct.** Dr. Francis W. Sovak. (For original article, see page 342.)

**Hormone Factors in the Toxemias of Pregnancy.** Drs. H. C. Taylor, Jr., and Eugene N. Seadron. (For original article, see page 963, June, 1939.)

**Studies on Reconstruction of the Fallopian Tube.** Dr. J. Randolph Gepfert. (For original article, see page 256.)

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## OBSTETRICAL SOCIETY OF PHILADELPHIA

*MEETING OF JANUARY 5, 1939*

The following papers and discussions were presented:

**Interstitial Pregnancy Following Salpingectomy.** Dr. Isador Forman. (For original article, see page 344.)

**Severe Menorrhagia as the Only Symptom of Essential Thrombocytopenic Purpura Cured by Splenectomy.** Drs. S. Leon Israel and Theodore H. Mendell (by invitation). (For original article, see page 339.)

**Report of a Series of Thirty-Five Cases of Primary Malignancies of the Ovaries.** Dr. Theodore Cianfrani (by invitation).

**Macrocytic Anemia of Pregnancy and Anemia of the Newborn.** Drs. Joseph A. Ritter (by invitation), and Walter J. Crocker (by invitation). (For original article, see page 239.)

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## CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF JANUARY 20, 1939*

The following papers were presented:

**The Obstetric Management of Patients with Toxemia.** Drs. W. J. Dieckmann and Ira Brown (by invitation). (For original article, see page 214.)

**The Treatment of Early Abortion.** Drs. C. E. Galloway and T. D. Paul. (For original article, see page 246.)

ciated with excessive extracellular fluid. The importance of sodium restriction in eclampsia has been emphasized by DeSnoo.<sup>10</sup> Strauss<sup>11</sup> has shown the beneficial influence of sodium restriction on both blood pressure and edema. Magnesium sulfate is of value as a diuretic; it appears to have a specific influence in reducing vasoconstriction and cerebral edema; it is of great value in controlling convulsions. As an adjunct to magnesium sulfate in sedation we prefer paraldehyde to morphine. Morphine causes too much respiratory depression, tending to produce anoxia which is decidedly undesirable for the reason that the concentration of blood observed by Dieckmann also tends to cause anoxia and myocardial embarrassment. We find that administration of oxygen is of definite value, for the fetus as well as the mother. Glucose in 10 per cent (sodium free) solution is administered intravenously as a heart tonic, to facilitate diuresis, and for calories.

#### SUMMARY

In eclampsia, as in nephrosis, there is an excessive activity in production of ammonia by the kidneys. It is suggested that excessive resorption of glomerular fluid is a contributory cause of scanty urine and edema in eclampsia.

The relation of the edema to certain clinical features of eclampsia is discussed.

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*Johnson, C. R.*: Pelvimetry by Stereoroentgenometry. Am. J. Roentgenol. 38: 607, 1937.

Stereoroentgenometry offers a practical method for the application of roentgenology in obstetrics. The obstetrician who depends upon external measurements of the maternal pelvis for his information as to deformity or contracture of the birth canal leans upon a weak staff. It is probable that if he guessed all his patients normal and made no measurements at all he would be right in a much higher percentage of cases. If he measures the diagonal conjugate and the bischial diameters by his best available clinical methods he will probably find those cases which might have dystocia. If he takes this latter group in which he finds clinical evidence of abnormality and has them subjected to careful roentgen study, he will find that about one out of every three actually have abnormalities and will require special attention. Stereoroentgenometry offers a method for determination of the solid dimensions of radiopaque objects from their stereoscopic roentgenograms. It is useful because it is practical.

J. P. GREENHILL.

up to twelve years of age. In this series, there were 221 spontaneous deliveries and 91 forceps operations. The author found that premature rupture of the membranes affects neither the maternal mortality nor the health and mentality of the offspring.

J. P. GREENHILL

**Smythe and Thompson:** Induction of Labor by Rupture or High Puncture of the Membranes, *J. Obst. & Gynaec. Brit. Emp.* 44: 480, 1937.

Induction is performed in one of two ways: The first is by simple rupture of the membranes at the internal os, and is done with or without anesthesia. A volsellum is employed to tear the membranes, and liquor allowed to drain by slightly pushing up the fetal head. In this way the amount can be roughly controlled.

The other method, viz., high puncture of the membranes, is performed as follows: One finger is inserted into the cervix and passed up until the head can be felt. The S-shaped cannula is then passed up the finger until it meets the head and then passed between the membranes and the uterine wall above the head when the membranes are punctured by pressing home the stylet. This can also be done with or without anesthesia, as indicated in each particular case. The special advantage of this method is that the chances of infection of the liquor are greatly diminished, which is of great importance should cesarean section become necessary in the course of a trial labor.

In the Bristol General Hospital series of 210 consecutive labors all the cases of induction by artificial rupture of the membranes at the os were successful and only one induction with the cannula failed.

The duration of labor is not appreciably lengthened. Stillbirth rate and the likelihood of sepsis are not increased. In this series 91.4 per cent of the cases had unassisted deliveries.

J. P. GREENHILL

**Thoms, Herbert:** The Obstetrical Significance of Pelvic Variations, *Brit. M. J.* 2: 210, 1937.

The report is given of an x-ray study of 450 primiparous white women delivered at term in the New Haven Hospital.

The "grid method" of pelvimetry originally developed by Thoms was used. In addition, lateral aspects of pelvic roentgenometry were employed, as well as a newly modified technique for lateral viewing.

The author classifies the pelvis into four types:

1. Dolichopellic or anthropoid type. The anteroposterior diameter is longer than the transverse.
2. Mesatipellic or round type. The anteroposterior diameter is equal to or slightly less than the transverse (never more than 1 cm.).
3. Brachypellic or oval type. The anteroposterior diameter is between 1 and 3 cm. shorter than the transverse.
4. Platypellic or flat type. The anteroposterior diameter is excessively shorter than the transverse, 3 cm. or more.

On the basis of the length of the anteroposterior diameter, the first three groups may be divided for clinical use into large, average, and small pelvis which classification serves to depict the shape of the superior strait. The external measurements bear no relation to those of the superior strait by roentgenometry.

The incidence of the various types is recorded. The author finds that the round type predominates.

This study calls for a reconstruction of views regarding normal white female pelvis, as evidenced by the presence of the oval or brachypellic type in only 35 per cent of cases. The chief value of roentgenometry is in cases of suspected disproportion. Here the lateral technique is of great importance.

Routine use of x-ray in primiparous women is justified and serviceable.

F. L. ADAIR AND S. A. PEARL

# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### Labor

Fredrikson, H.: The Effect on Deliveries of Spontaneous Rupture of the Membranes, *Aeta obst. et gynec. Scandinav.* 17: 309, 1937.

The author studied 1,290 primiparas and 1,300 multiparas who had normal occipitoanterior presentations in which the babies weighed over 2,500 gm., to determine the effect of spontaneous rupture of the membranes on labor. As "premature rupture" he designates cases in which rupture occurred before or simultaneously with the onset of pains. The term "early rupture" is used to indicate rupture of the bag of waters after the onset of pains but before the cervix is dilated to the size of three fingers. The author found that rupture of the membranes occurred before the onset of pains in 12 per cent of primiparas and in 10.7 per cent of multiparas. Rupture of the bag of waters occurred simultaneously with the onset of pains in 7.8 per cent of primiparas and in 5.7 per cent of multiparas. In both primiparas and multiparas the duration of labor was considerably shortened in cases of premature rupture of the membranes. In primiparas, labor was definitely prolonged in cases of early rupture. Genital infections during labor occurred twice as often in cases of premature and early rupture as in the cases of late rupture. The fetal mortality was not increased in cases of premature rupture, but it was higher in cases of early rupture.

J. P. GREENHILL

Apajalahti, A.: Is the Time of Rupture of the Membranes Dependent Upon the Histologic Structure of the Membranes? *Aeta obst. et Gynec. Scandinav.* 18: 57, 1938.

This investigation verifies the fact that rupture of the bag of waters during labor bears a definite relation to the histologic structure of the fetal membranes especially to the thickness of the amnion. The thinner the membranes are, especially the amnion, the more pronounced are the degenerative changes, and the easier it is for the membranes to rupture. The author could not find any evidence that inflammation produced any adhesions between the membranes and the decidua.

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Wetterdal, P.: Some Notes on the Premature Rupture of the Membranes, *Aeta Obst. et Gynec. Scandinav.* 18: 45, 1938.

The author studied a series of 1,022 cases in which liquor amnii was expelled before the onset of labor pains. He found two classes of patients. In the first group labor was short and there were few complications, while in the second group delivery was delayed and there were numerous complications. The author believes that the responsible factor for the complications in the second group is not the premature rupture of the bag of waters but the ineffectual labor pains which occur in this series.

A vaginal examination in 150 cases of premature rupture of the membranes revealed that in some of these cases a certain amount of labor had occurred without the patient's knowledge. In a series of 312 cases of premature rupture of the membranes the author not only studied the mothers but also the children



Babies weighing 4,000 gm. and more were born to 24.7 per cent of the overweight group and to only 4.4 per cent of the control series. The fetal mortality in these two groups was 6.7 per cent and 0.6 per cent, respectively.

J. P. GREENHILL

Reist, A.: Significance of Manual Dilation of Os Uteri in Treatment of Disturbances in Dilatation of Soft Parts During Birth, *Schweiz. med. Wchnschr.* 66: 1176, 1936.

If a careful technique is employed and asepsis is preserved, manual dilatation of the os uteri produces in suitable cases the desired results, that is, rapid termination of the period of dilatation. It is helpful in certain cases in which dilatation is retarded or has completely stopped, because it permits spontaneous delivery in a manner that involves no danger for either mother or child. Manual dilatation of the os uteri can be used also for rapid opening of the soft parts for the purpose of an immediate delivery in cases in which danger appears suddenly for either mother or child. Reist uses this procedure in 4-6 per cent of all deliveries. Its correct employment reduces the number of extensive vaginal obstetric interventions as well as infant mortality during birth.

J. P. GREENHILL

Taylor, H. C., Jr.: Indications and Technic of Episiotomy, *Am. J. Surg.* 35: 403, 1937.

Correct use of episiotomy forms one of the niceties of obstetric practice. The consideration of whether to undertake the operation in a given case demands balancing of a known type of surgical injury against an unknown degree of trauma from the stretching effects of the presenting part against the perineum. Regret for having performed needless episiotomy is probably less frequent and certainly less permanent than that experienced at times for having omitted it.

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Jahier: Fifty-Seven Breech Deliveries, *Bull. Soc. d'obst. et de gynéc.* 26: 615, 1937.

Among the 57 breech presentations reported by the author there were 35 primiparas and 22 multiparas. There was no maternal mortality in this series but three babies were lost. The author makes a few recommendations. Among these are that two obstetricians be present in cases where difficulty is expected, so that they may take turns in executing the delicate maneuvers necessary for delivery of the child. An episiotomy should be done routinely and in many cases it should be bilateral. The author recommends that thin gloves be used and that they should be well lubricated. He also urges that all equipment be at hand for the resuscitation of the newborn.

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Macafee, C. H. G., and McClure, H. I.: A Critical Survey of 349 Cases of Breech Delivery, *Brit. M. J.* 2: 1112, 1937.

Three hundred and forty-nine cases of breech delivery formed the basis for the following conclusions: 305 were primary breech presentations. In all, 332 mothers were delivered of 349 babies, i.e., there were seventeen cases of twins in which each child was delivered by breech. Outside of 3 cesarean sections, all deliveries were performed by usual methods. The gross fetal mortality was 33.8 per cent, being 23.72 for primiparas and 38.96 per cent for multiparas. Corrected rates, eliminating those cases in which the death of the fetus was not primarily or directly due to the breech presentation, gave a 10 per cent fetal mortality for primiparas and 3.42 per cent for multiparas.

Greulich, W. W., and Thoms, Herbert: *The Dimensions of the Pelvic Inlet of 789 White Females*, *Anat. Rec.* 72: 45, 1938.

More or less coinciding with the dimensions given in most textbooks, more recently, Jarchow (1933) from a compilation of several large series of measurements of pelves of European women concluded that a conjugate of from 11.0 to 11.5 cm. and a transverse diameter of 13.5 cm. for the pelvic inlet may be considered as normal.

Such dimensions so far had been determined on cadavers and dried pelves. In the belief of the authors methods of roentgen pelvimetry have developed now to such a degree of exactness that dimensions obtained in this manner must be accepted as accurate. The authors summarized their findings in approximately 600 primigravidas and 100 nulliparous, well-developed young women (student nurses).

Their results are striking. In 37 per cent of nurses the conjugate of the inlet was larger than the transverse diameter. This same relation was ascertained, e.g., among 132 clinic patients, in only 13.6 per cent. The transverse diameter exceeded the conjugate by more than 1 cm. in only 17 per cent of the nurses as compared with 40.1 per cent among clinic women. In only 6 per cent of the nurses and 14.9 per cent of the clinic patients the excess of transverse over conjugate diameter was more than 2 cm., and thus large enough to fit the textbook description of the "normal" pelvis.

Some of the final conclusions are of interest to the obstetrician.

The type of pelvis, which for the past two centuries has been considered normal for white women, was found in less than 15 per cent of 582, primiparous clinic patients, and in only 6 per cent of 100 young women from a much more privileged economic group. It was, therefore, neither the normal pelvis, in the sense of being the most frequently occurring type, nor was it the most adequate type, as gauged by the relative frequency of operative interference required during labor.

It has been known for a long time that marked anterior-posterior flattening of the adult pelvis may result from severe rickets during early life. The high incidence of round and of antero-posteriorly elongated pelves among the nurses suggests the possibility that adequate nutrition during early life and other factors which make for attainment of maximum, normal body size prevent that degree of anteroposterior flattening of the pelvis which has come to be regarded as characteristically feminine.

HUGO EHRENFEST

Moller-Christensen, E.: *The Course of Pregnancy, Labor, and Puerperium in Overweight Primiparas*, *Acta obst. et gynec. Scandinav.* 18: 222, 1938.

A series of 242 overweight primiparas was studied by the author, who considered a woman overweight if at the end of pregnancy she weighed at least 20 per cent more than a nonpregnant woman of her age and height. He compared this series with another consisting of 500 women not one of whom weighed over 70 Kg. (154 pounds). The author found ordinarily that obese patients are more frequently sterile than women with normal weights. Nephritis occurred in 21.4 per cent of the overweight women and eclampsia in 7.2 per cent. On the other hand nephritis occurred in only 1.6 per cent of the women with normal weights and there was not a single case of eclampsia in the latter group. Hypertension occurred in 6.2 per cent and 0.4 per cent, respectively, in the two groups. Likewise pyelitis was found in 11.6 per cent of the overweight group and in only 4.8 per cent of the control group.

During labor there were more complications in the overweight group, especially uterine atony. These lead to a greater frequency of post-partum hemorrhage, retained placentas, and manual removal of the placenta.

Labor lasted, on an average, 27½ hours in the overweight women and only 13½ hours in the others. Uterine atony occurred in 18.4 per cent and 4.4 per cent, respectively, of the author's cases. Premature rupture of the membranes occurred in 14.8 per cent and 4 per cent, respectively. Fever occurred in 8.7 per cent and 0.6 per cent, respectively.

McIlroy, Louise: *Surgical Intervention in Obstetrical Practice*, Brit. M. J. 1: 800, 1937.

A brief discussion is given of the indications for and against surgical intervention in obstetric practice from the standpoint of the general practitioner. The wider the experience one has gained in the management of obstetric cases, the more conservative one generally becomes.

Maternal mortality records from all parts of the world prove that conservative methods in obstetrics furnish the most favorable results. Not infrequently many an obstetrician has faced the problem of gathering courage to leave well enough alone, rather than terminate pregnancy or labor by some operative method. The author's rule is "when in doubt do nothing," and "wait and see" is not a bad rule to follow in obstetrics. It is the exercise of wise judgment, however, that really gives good results.

Antenatal complications are discussed. Intervention during labor, the management of the third stage, and puerperal sepsis are treated briefly.

F. L. ADAIR AND S. A. PEARL.

Stapleton, Grace: *Rupture of the Pregnant Uterus From Indirect Injury*, Brit. M. J. 2: 367, 1937.

The author reports a case of complete rupture of the uterus from indirect injury in a primigravida of 17 years. The fall from a 12 foot high veranda occurred some ten days before term. The patient was ill for several days in bed with vomiting and slight pain but later showed no alarming symptoms of a grave injury. The patient failed to go into labor after two medical inductions at which time the correct diagnosis was established. Laparotomy with extraction of the baby from the abdominal cavity and subsequent rapid repair of the ruptured uterine wall was followed by recovery, although surgery was undertaken fourteen days after the injury. The patient did not show the classical signs and symptoms of a ruptured uterus.

F. L. ADAIR AND S. A. PEARL.

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## Items

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### American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 6, 1940, at 2:00 P.M. *The Board announces that it will hold only one Group B, Part I, examination this year prior to the final general examination, instead of two as in former years.* Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held in June, 1940.

Applications for admission to Group B, Part I, examinations must be on file in the Secretary's office not later than October 4, 1939.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J., on June 8, 9, 10, and 11, 1940, immediately prior to the annual meeting of the American Medical Association in New York City.

Applications for admission to Group A, Part II examinations must be on file in the Secretary's office not later than March 15, 1940.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I examinations (written paper and case records) and the Part II examinations (pathological and oral).

In summarizing their management of breech presentation, they strongly recommend external version after the thirtieth week in all cases and not later than the thirty-fourth in multiparas.

In breech delivery the authors interfere only when the breech has ceased to advance. Episiotomies are done on all primiparas and when necessary in multigravidas. They urge that the operator refrain from interfering with normal mechanisms pointing out that slow and gentle deliveries prevent tentorial tears, and these tears are much more likely to cause death of the fetus than asphyxia, the excuse for rapid delivery.

F. L. ADAIR AND J. A. HAUGEN.

**Chamanlal Mehta:** External Version for Breech Presentations, Brit. M. J. 1: 706, 1937.

The author presents an analysis of 5,028 deliveries in which two groups are discussed. Group I consists of 3,240 deliveries in which breech presentation was recognized and not interfered with during pregnancy. Eighty-eight women were confined as breech deliveries, an incidence of 2.7 per cent, and the fetal mortality in this group was 37.5 per cent. Of the 88 breech presentations 21 were in primiparas, with a fetal mortality of 33.3 per cent and 67 in multiparas with a fetal mortality of 38.8 per cent.

In the second group of 1,788 consecutive deliveries, breech presentation was diagnosed in 110 cases, but only 11 of them became breech deliveries, i.e., 0.06 per cent. Fifty-five were treated by external version during pregnancy. The fetal mortality in this series of 110 cases was 4.54 per cent, and all the deaths were in the untreated cases. There was no mortality in the cases managed by external version. The fetal mortality of 37.5 per cent in Group I should be compared with that of 4.54 per cent in Group II with no mortality in cases treated by external version.

The questions of prematurity, when to perform external version, its possible dangers and the technic are briefly discussed.

F. L. ADAIR AND S. A. PEARL.

**Casalta:** External Version Followed by Abruptio Placentae, Bull. Soc. d'obst. et de gynec. 27: 73, 1938.

The author reports a case of breech presentation in which he performed an external version. This was done very gently and the fetal heart tones were normal after the procedure. However six hours later the patient had uterine contractions and a profuse hemorrhage. The uterus became hard and a few hours later a still-born child was born. Two large clots were found in depressions in the placenta.

The author believes that the external version resulted in the separation of the placenta and death of the baby.

J. P. GREENHILL.

**Bruecke, H. v.:** High Forceps Operations, Arch. f. Gynäk. 164: 42, 1937.

An analysis of 18,611 deliveries in the Graz Frauenklinik showed a total forceps incidence of 2.1 per cent and a high forceps incidence of 0.18 per cent (34 cases). Among these latter 34 women there was no maternal mortality, but five suffered extensive lacerations of vagina and rectum, and two developed vesicovaginal fistulas following pressure necrosis in one and laceration in the other. Both fistulas healed spontaneously. Fourteen of the 34 babies died and 11 had severe head injuries. Most of these occurred in women with contracted pelves. In spite of the above results, the author believes that there is a definite even though only occasional indication for high forceps delivery. In such instances the Kielland forceps are the instruments of choice.

RALPH A. REIS.

**DIE ALLGEMEINBETAEUBUNG NACH IHREM HEUTIGEN STAND.** Dr. Richard Goldhahn, Chefarzt des Kreiskrankenhauses Liegnitz. With 10 illustrations, 79 pages. Verlag von Ferdinand Enke, Stuttgart, 1939.

**GYNAECOLOGY.** By Herbert H. Schlink, Lecturer and Examiner in Gynaecology, University of Sydney, etc. 179 illustrations, 557 pages. Angus & Robertson Limited, Sydney, 1939.

**A TEXTBOOK OF OBSTETRICS,** With Special Reference to Nursing Care. By Charles B. Reed, Associate Professor of Obstetrics, Northwestern University Medical School, etc., and Bess I. Cooley, R. N., Supervisor and Instructor, Department of Obstetrics, Wesley Memorial Hospital, Chicago. With 209 illustrations, 476 pages. The C. V. Mosby Company, St. Louis, 1939.

**THE CLINICAL AND EXPERIMENTAL USE OF SULFANILAMIDE, SULFAPYRIDINE, and Allied Compounds.** By Perrin H. Long, M.D., Associate Professor of Medicine, School of Medicine, Johns Hopkins University, etc., and Eleanor A. Bliss, Sc.D., Fellow in Medicine, Johns Hopkins University. 319 pages. The Macmillan Company, New York, 1939.

**HANDSCHRIFT UND EIGENART DER KREBSGEFAEHRDETEN.** Ein Beitrag zur Dispositionsforschung. Illustrated, 297 pages. Verlag von Brueder Tisza, Budapest, Hungary. (T. H. McKenna Inc. 878 Lexington Ave., New York, N. Y.).

**SYPHILIS, and Its Accomplices in Mischief: Society, State and Physician.** By George M. Katsainos. Privately printed at Athens, Greece. 1939.

**DIE KREUZSCHMERZEN DER FRAU.** Ihre Deutung und Behandlung, Gynäkologische Orthopaedie. Von Professor Dr. Heinrich Martius, Direktor der Universitaets-Frauenklinik in Goettingen. With 64 illustrations, 179 pages. Verlag von Georg Thieme, Leipzig, 1939.

**POPULATION, RACE AND EUGENICS.** By Morris Siegel, M.D. 206 pages. Published by the author, 546 Barton St., East Hamilton, Ontario, 1939.

**MENSTRUAL DISORDERS.** Pathology, Diagnosis and Treatment. By C. Frederic Fluhmann, Associate Professor of Obstetrics and Gynecology, Stanford University, School of Medicine, San Francisco, etc. 119 illustrations, 329 pages. W. B. Saunders Company, Philadelphia, 1939.

**DIE INTRAKRANIELLEN BLUTUNGEN BEI NEUGEBORENEEN.** Von Professor Dr. Erwin Kehr. Direktor der Universitaets-Frauenklinik in Marburg. With 20 illustrations including 2 color plates and 1 Table, 79 pages. Verlag von Ferdinand Enke, Stuttgart, 1939.

**DER ANEURIN (VITAMIN B 1) HAUSHALT IN DER SCHWANGERSCHAFT UND IM WOCHENBETT.** Von Gerhard Gaeltgens, Leipzig. With 7 illustrations, 76 pages. Verlag von Georg Thieme, Leipzig, 1939.

**NORMALE UND PATHOLOGISCHE PHYSIOLOGIE IM WASSERHAUSHALT DER SCHWANGEREN.** Von Dr. Herbert Albers, Leipzig. With 25 illustrations, 119 pages. Verlag von Georg Thieme, Leipzig, 1939.

**CANCER OF THE BREAST AND CANCER OF THE UTERUS.** By Marion Ellsworth Anderson, M.D., Clinton, Ohio. Franklin Press, Clinton, Ohio, 1939.

**LIFE AND LETTERS OF DR. WILLIAM BEAUMONT.** By Jesse S. Myer, M.D., Late Associate in Medicine in Washington University, St. Louis. With an Introduction by Sir William Osler. The C. V. Mosby Company, St. Louis, 1939.

**CANCER HANDBOOK** of the Tumor Clinic, Stanford University School of Medicine. Edited by Eric Liljewerantz, Chief of Tumor Clinic, etc. 50 illustrations, 114 pages. Stanford University Press. California, 1939.

At the annual meeting of the Board, held in St. Louis on May 12, 1939, it was found necessary, on account of increased administrative expenses, to increase the application and examination fees. Effective May 12, 1939, these are as follows: Application fee \$15.00, payable upon submission of application for review by Board; examination fee \$85.00, payable upon notification to candidate of acceptance of the application and assignment to examination. Neither fee is returnable. This increase does not apply to candidates whose applications were filed prior to May 12, 1939.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

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### Pacific Coast Society of Obstetrics and Gynecology

The dates for the next meeting of the Pacific Coast Society of Obstetrics and Gynecology have been changed from October 4 to 7, 1939 to November 8 to 11, 1939 in Portland, Oregon.

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### Central Association of Obstetricians and Gynecologists

The Eleventh Annual Meeting of the Central Association of Obstetricians and Gynecologists will be held at the Hotel Muehlebach, Kansas City, Mo., November 2, 3, and 4, 1939. The guest speaker will be Dr. Edward A. Schumann, of Philadelphia, Pa.

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## Books Received

**THE GENUINE WORKS OF HIPPOCRATES.** Translated from the Greek by Francis Adams, LL.D., Surgeon. The Williams & Wilkins Company, Baltimore, 1939.

**RECENT ADVANCES IN OBSTETRICS AND GYNAECOLOGY.** By Aleck W. Bourne, Obstetric Surgeon to St. Mary's Hospital, etc., and Leslie H. Williams, Senior Obstetric Surgeon to Out-Patients, St. Mary's Hospital, etc., University of Cambridge. Fourth edition, with 98 illustrations, 366 pages. Blakiston's Son & Co., Philadelphia, 1939.

**CLINICAL PATHOLOGICAL GYNECOLOGY.** By J. Thornwell Witherspoon, Formerly Associate Professor of Experimental and Pathological Gynecology, Indiana University Medical Center, Indianapolis. Illustrated with 271 engravings, 400 pages. Lea & Febiger, Philadelphia, 1939.

**TEXTBOOK OF GENERAL SURGERY.** By Warren H. Cole, Professor of Surgery, University of Illinois, College of Medicine, etc., and Robert Elman, Associate Professor of Surgery, Washington University School of Medicine, St. Louis. Second edition, 559 illustrations, 1031 pages. D. Appleton-Century Company, New York, 1939.

**SEX AND INTERNAL SECRETIONS.** A Survey of Recent Research. Editors: Edgar Allen, Yale University; Charles H. Danforth, Stanford University; and Edward A. Doisy, St. Louis University, with foreword by Robert M. Yerkes, Yale University. Second edition, illustrated, 1346 pages. Williams & Wilkins Company, Baltimore, 1939.

**VERHUETUNG ERBKRAKEN NACHWUCHSES.** Eine kritische Betrachtung und Wuerdigung. Herausgegeben von Dr. St. Zurukzoglu. 346 pages. Verlag von Benno Schwabe, Basle, 1938.

**ENDOCRINOLOGY IN MODERN PRACTICE.** By William Wolf, Endocrinologist to the French Hospital, etc. Second edition, completely revised. 176 illustrations, 1077 pages. W. B. Saunders Company, Philadelphia, 1939.

This study concerns itself with a simplified improved technique for the titration of estrogenic and gonadotropic hormones in the serum of pregnant women, which proved to be useful in following the concentrations of these hormones in normal gestation, together with similar studies in a number of the complications of pregnancy, especially in the toxemias and abortion.

### METHODS

Early in this study determinations of the estrogenic and gonadotropic hormones were made in both the urine and serum of pregnant women. Preliminary studies made at daily intervals soon revealed that much more constant results were obtained from the blood serum than from twenty-four-hour urine specimens, although the values followed each other in a rough fashion. This was probably the result of a number of factors, including errors inherent in the extraction of the hormones from the urine, the presence of the hormones in several conjugated forms in the urine, difficulty in obtaining accurate twenty-four-hour outputs in ambulatory patients, and perhaps variations due to a mechanism regulating the concentration in the tissues. It was felt that titrations of the blood serum were much more likely to be applicable for routine clinical use, and that the information obtained would be of greater significance than urinary titrations, although it must be admitted that the latter furnishes information of additional value.

Although some studies have been reported on the concentration of estrogenic and gonadotropic substances in whole blood and serum during pregnancy, their number and accuracy have been limited by the large quantities of blood which were necessary for the biologic tests employed. This difficulty was apparently the result of the loss of most of the hormone by extraction methods, and the use of rats rather than mice as test animals, thus requiring larger amounts of serum and permitting the use of fewer animals.

By using the unextracted sera as the test solutions and mice as the test animals a simplified technique for biologic titrations was developed by which reliable results are obtainable with from 20 to 50 c.c. of blood, depending upon the period of gestation.

*Estrogenic Hormone.*—A modification of Fluhmann's technique<sup>2</sup> was employed. The test animals were young, adult, castrated mice of about eight weeks of age and 25 gm. in weight, which were used exactly seven days after castration. Atrophy of the vaginal wall was confirmed by examining smears for two days before use. Whole or diluted serum was injected subcutaneously in 6 divided doses over a period of three days. The animals were sacrificed on the fourth afternoon and biopsies were taken from the middle portion of the vagina. Histologic sections were prepared by a rapid technique and stained with hematoxylin and eosin. The least amount of serum which produced complete hyperplasia to vaginal cornification (Reactions 4 to 5, Fluhmann) was regarded as containing one mouse unit. Also the uterine cornua were examined macroscopically for estrus, since with this technique macroscopically positive uteri indicated dosages several times the amount necessary to produce vaginal cornification.

For the initial titration 3 to 6 animals were injected with varying amounts of serum. When the approximate quantity necessary to produce cornification was found, 3 to 6 additional animals were injected with more closely grouped dosages. Further titrations were conducted if necessary. Six to twelve animals were generally used for each titration, while 3 to 6 animals were injected with dosages very close to the finally accepted value. With the histologic technique and the use of a total of 3 animals for a given dose range, quite reliable results were obtained which were far superior to those offered by the vaginal smear method.<sup>3</sup> With experience the final dosage can be closely approximated from the partial reaction obtained with smaller quantities, while dosages which produce full uterine estrus are usually at least three times too great.

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## Original Communications

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### STUDIES ON THE CONCENTRATIONS OF ESTROGENIC AND GONADOTROPIC HORMONES IN THE SERUM OF PREGNANT WOMEN\*

A. E. RAKOFF, M.D., PHILADELPHIA, PA.

*(From the Department of Obstetrics, Jefferson Medical College Hospital)*

THE significance of the manifold changes in the sex hormones which occur during pregnancy remains largely an enigma, chiefly because of the complexity of the hormonal variations, the difficulties attendant upon their quantitative estimation, and an incomplete knowledge of their metabolism. Nevertheless, the scant information which has been derived from even the crude methods of study available has proved to be of considerable value, as for example in the establishment of a diagnosis of pregnancy, presumptive evidence of fetal death, or the presence of tumors arising from chorionic tissue.

Increasing evidence that a number of other complications and abnormalities of pregnancy are associated with, if not actually related etiologically to, variations in the concentrations of the sex hormones, has lent clinical significance to the quantitative estimation of these substances in the body fluids and tissues of the gravid woman.

Unfortunately, however, many such studies are based on rather scant laboratory data. Indeed studies of the sex hormone values in normal pregnancy are surprisingly few. Furthermore such scant data are hardly applicable to general use, since it is well known that discrepancies in biologic titrations obtained in different laboratories are often so great, owing to differences in test animals, technique and interpretation, as to make comparative results unreliable. It is desirable therefore for each obstetric laboratory engaging in hormonal titrations to establish for itself a set of normal values based on a standardized technique.

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\*Presented at a meeting of the Obstetrical Society of Philadelphia, March 2, 1939.

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NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."



that our values were roughly twenty times higher. This is undoubtedly due to loss of the hormone by extraction, since it has been demonstrated by Kemp and Bjergaard<sup>7</sup> that the blood estrin is practically equally divided between the corpuscles and the plasma.

Before the eighth week of pregnancy a full mouse unit usually cannot be demonstrated in less than 4 c.c. of serum, while in some instances the amount of serum containing a full mouse unit was greater than was tolerated by the animal, so that values were estimated by interpolation from partial reactions. Between the eighth and tenth weeks there was an average of 24 M.U. per 100 c.c. Thereafter the concentration continued to rise steadily. From the fourteenth to the twentieth weeks, many patients exhibited a sudden sharp rise which frequently coincided with the sudden fall in gonadotropic substance at this time. Another sharp rise often oc-

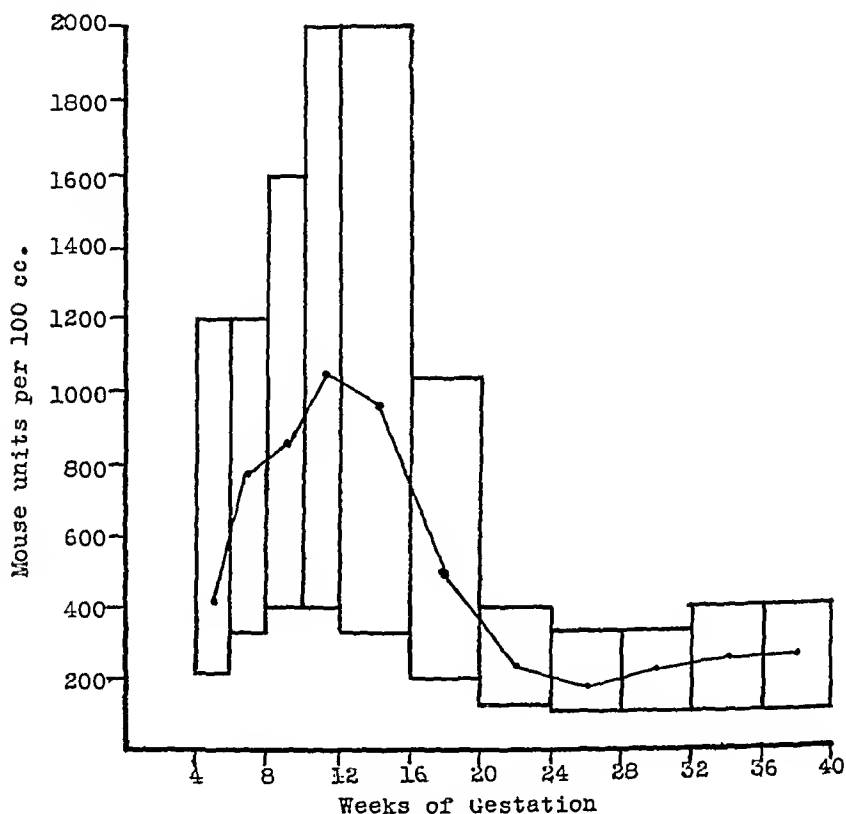


Fig. 2.—Serum prolactin in normal pregnancy. Composite graph of 162 determinations among 40 patients. Rectangles represent range of values, curve represents average values.

curs between the thirty-second and thirty-sixth weeks. At term more than 500 M.U. per 100 c.c. of serum is frequently present, perhaps in preparation for the large amounts which seem to be necessary to sensitize the uterus for the onset of labor.

The present consensus is that from almost the very beginning of pregnancy the estrogenic hormones are formed by the placental tissue; the latter structure according to Newton<sup>8</sup> and Collip<sup>9</sup> contains two and perhaps three estrogenic substances in high concentration. Thus even after double oophorectomy in early pregnancy the secretion of estrogens continues.

The nature and source of the gonadotropic hormones, which increase so rapidly in the serum in early pregnancy and are excreted in the urine in quantities sufficient to give a reliable test for pregnancy, within two weeks after the first missed period, has long been the subject for controversy. These have been assumed to be formed by the placenta because of the constant association of trophoblastic tissue with

*Gonadotropic Hormone.*—A modification of the Aschheim-Zondek test was used for the determination of gonadotropic substances. Whole or diluted sera were injected in 6 divided doses over a period of three days into infantile mice, approximately seventeen days old and 8 to 10 gm. in weight. The animals were sacrificed on the fifth morning. The least amount of serum which would cause the production of corpora hemorrhagica or corpora lutea in 2 of 3 animals was considered as containing one mouse unit (Reaction 2 and 3, Zondek<sup>4</sup>). The ovaries were inspected with the aid of a hand lens, but any suspicious specimens were sectioned for histologic examination. It was found expedient to recognize either corpora hemorrhagica or corpora lutea as end points in these titrations, because in some specimens the amount of follicle-stimulating hormone could be detected in higher dilutions of serum than could the luteinizing factor, although it must be recognized that their clinical significance may prove to be quite different. Increase in ovarian weight was not considered as a reliable means of titration, since the gonadotropic substance of pregnancy serum apparently causes only a limited increase.<sup>5</sup>

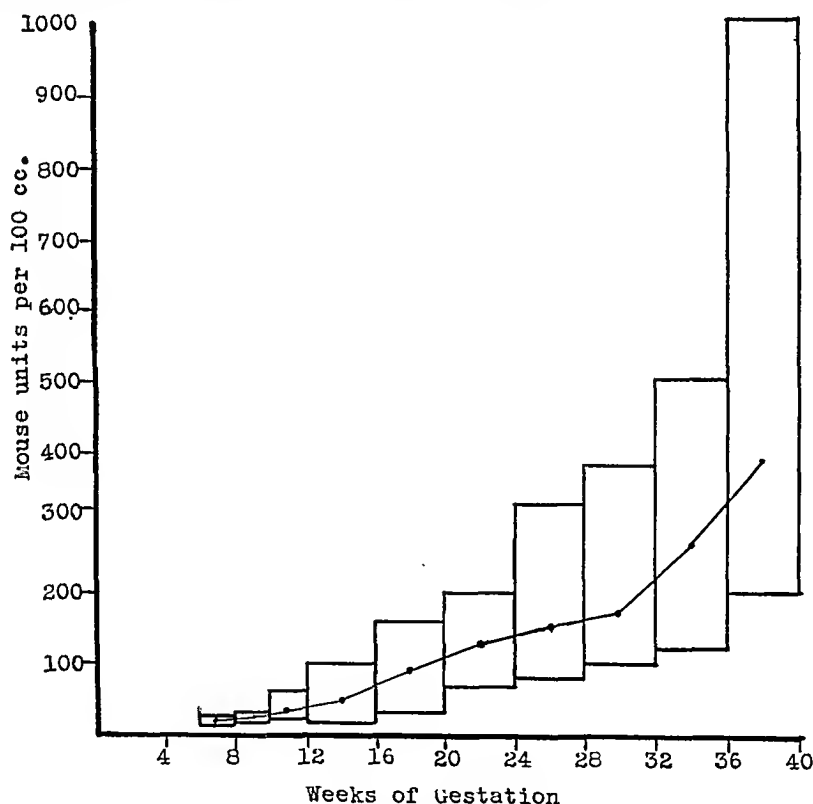


Fig. 1.—Serum estrogen in normal pregnancy. Composite graph of 162 determinations among 40 patients. Rectangles represent range of values, curve represents average values.

In further studies in early pregnancy, we have found concentrations of over 3,000 M.U. in several patients between the sixth and tenth weeks of gestation, indicating that the values for this period are considerably higher than given above. Apparently in some patients a peak is reached some weeks earlier than in others.

## RESULTS

1. *Normal Pregnancy.*—Composite graphs were prepared of the values for serum estrogen on 162 determinations among 40 normal pregnant women in various stages of gestation, each patient being tested every two to four weeks for periods of two to six months (Fig. 1).

Preliminary data<sup>1</sup> have been presented of our titrations of the estrogenic content of unextracted blood serum in various stages of pregnancy. These correspond roughly with the results obtained on extracted whole blood by Smiths except

It has been pointed out that the rapid rise in concentration of prolactin which occurs between the sixth and eighth weeks of pregnancy corresponds to the time when the fetal circulation is established in the chorionic villi, and that it reaches its peak just about the time when the ovary apparently becomes superfluous. Between the tenth and sixteenth weeks of normal pregnancy we have demonstrated the presence of as much as 2,000 M.U. per 100 c.c. of serum. Newton<sup>8</sup> postulates that this may represent a "mass attack" on the ovary to inhibit the follicular system, since the corpus luteum, which probably checks cyclic changes in the first weeks, would probably be incapable of doing so later on.

In the latter half of normal pregnancy the prolactin content remains essentially unchanged, although it is in the last trimester in which high values seem to be indicative of dysfunction.

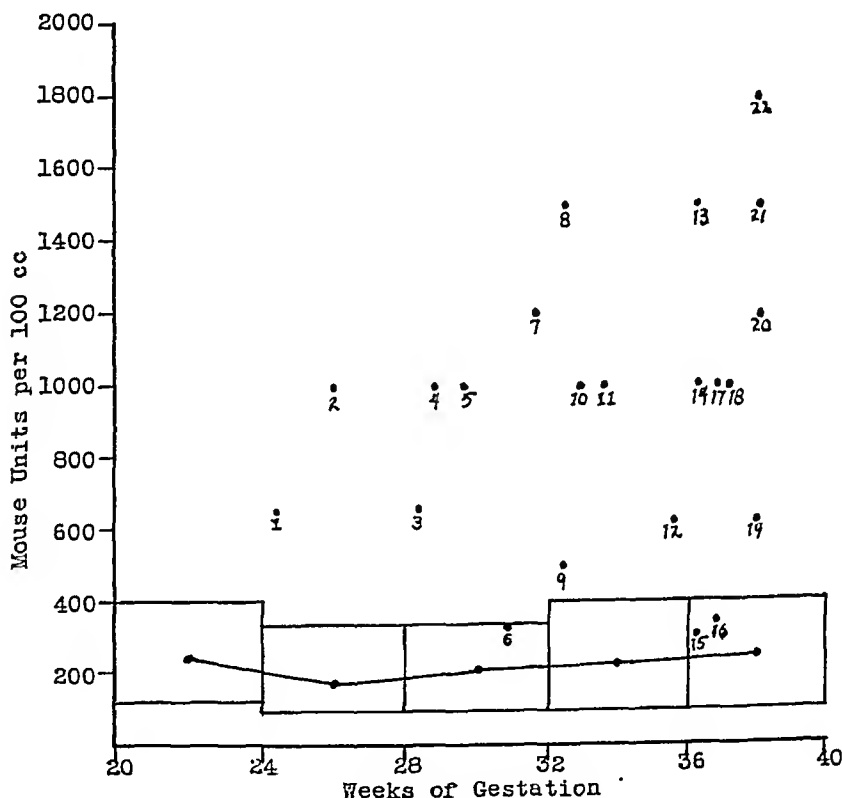


Fig. 4.—Serum prolactin in toxemias of late pregnancy. Numbered dots represent same patients as in Fig. 3.

#### TOXEMIAS OF PREGNANCY

Variations in the sex hormones have not been left unchallenged as an etiologic factor in the toxemias of pregnancy.

Shute<sup>17</sup> has contended that the majority of severe toxemias of late pregnancy, except those of the eclamptic type, are associated with excessive quantities of estrogenic hormone. His statements are based on the detection of excessive quantities of estrogenic substances (in the blood serum) by means of a test utilizing the proteolysis of blood serum.<sup>18</sup> It is stated that when excessive quantities of estrin are present the proteolysis of blood serum by trypsin is inhibited. We have not been able to confirm Shute's work in our laboratory, nor does it seem logical to us that such a test can indicate quantities of estrogen that are "excessive" at any given period when the normal concentration during pregnancy is continually rising.

large quantities of gonadotropic substance. As Newton<sup>8</sup> points out, not only does the latter rapidly disappear from the urine and blood after parturition, but in case of incomplete abortion, it persists until all placental remnants have been delivered.

It remained however, for Nagayama,<sup>10</sup> in a recent report to demonstrate the production of gonadotropic hormone, *in vitro*, in placental tissue cultures. This has been confirmed by Gey and his associates<sup>11</sup> who also found that tissue from a hydatidiform mole grown in culture produced the hormone. It is interesting that Nagayama<sup>10</sup> found no significant quantities of gonadotropic hormone in tissue cultures of the anterior hypophysis of the pregnant rabbit.

Whether the placental gonadotropic substance, which has been termed anterior pituitary-like, differs in any important essential from that of hypophyseal origin has been seriously questioned. The early report of Reichert,<sup>12</sup> which stated that ovulation did not occur in hypophysectomized rats injected with pregnancy prolan, is not in agreement with subsequent work of Smith and Leonard,<sup>13</sup> Zondek,<sup>14</sup> Hill and Parkes,<sup>15</sup> and others.

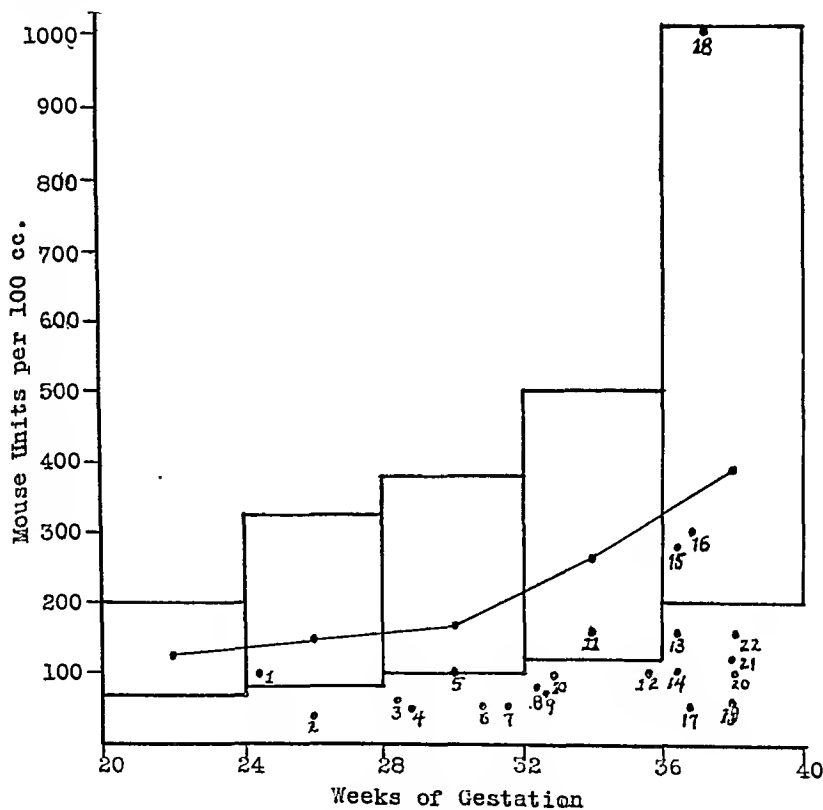


Fig. 3.—Serum estrogen in toxemias of late pregnancy. Rectangles represent range of values in normal pregnancy, curve represents average values in normal pregnancy, numbered dots represent values in toxemias of late pregnancy.

It has been shown that the serum of pregnancy may be used without extraction for the titration of gonadotropic hormone throughout gestation. The character of the curve of the average values is similar to that obtained from extracts of the serum by Boycott and Rowlands,<sup>5</sup> and Smith and Smith.<sup>16</sup> The latter workers state that they employed extracts of the sera and urines for titrations of gonadotropic substances, because they found the injected material to be toxic for immature animals. We have experienced this difficulty in using unextracted urine specimens, but have rarely noted it in the small quantities of sera required for each test during pregnancy. Our values for serum prolau are generally from five to ten times those noted by Smith and Smith on extracted specimens.

Here the manner in which the serum prolactin and estrogen were correlated with the clinical course was more apparent. In one instance abnormally high values preceded the clinical onset of toxemia by three weeks. In another patient who was being studied for repeated miscarriages, high prolactin values also preceded the onset of a moderately severe pre-eclamptic toxemia.

*Nephritic Toxemia.*—Three patients with nephritic toxemia were available for study, of which two deserve special mention.

CASE 1.—G. T., colored, aged 42 years, gravida ix, registered in the sixth lunar month of pregnancy with a history of severe nephritic toxemia in her last pregnancy. The blood pressure was 192/118, albumin +++, and hyaline and granular casts were present in the urine. Nonprotein nitrogen was 91 mg., creatinine 5.1 mg., and uric acid 5.44 mg. per 100 c.c. Urea clearance was 13 per cent average normal. Liver function tests were normal.

The serum prolactin was elevated to 1,200 M.U. and remained the same on a second examination one week later. Serum estrogen was moderately low on the first examination (50 M.U. per 100 c.c.) and had fallen to 33 M.U. on the second examination.

This patient signed her release from the hospital refusing further treatment. Two months later she developed eclampsia post partum and died.

CASE 2.—M. H., colored, aged 18 years, gravida ii, registered in the fourth lunar month of pregnancy with a history of nephritic toxemia and eclampsia in the last pregnancy one year earlier. In the interim she had been under treatment for syphilis and glomerulonephritis. The blood pressure throughout pregnancy ranged from 96/48 to 134/80. There was a consistent mild albuminuria and occasionally red blood cells and casts in the urine. The liver and kidney functional tests were normal. By rigid prenatal care this patient was carried along to term with only one admission to the hospital for impending nephritic toxemia, although there were signs and symptoms of mild toxemia throughout the pregnancy. Serum estrogen and prolactin were titrated at frequent intervals, and it is significant that both deviated from the normal range on only two occasions, coinciding with exacerbations in the patient's condition.

Hormone studies were not conducted on the third patient until she was readmitted to the ward at the seventh lunar month with an exacerbation of nephritic toxemia for the fourth time during the gestation. Her serum prolactin was very low, 50 M.U. per 100 c.c., which was accounted for by the fact that two days later she was delivered of a macerated fetus.

Indeed we have found that wherever fetal death is suspected, especially in patients with threatened abortion, the quantitative serum prolactin determinations repeated at frequent intervals furnished a reliable indication as to the prognosis for the fetus. A continual fall in the serum prolactin below the normal range usually indicated death of the fetus, despite the fact that the Friedman test may remain positive for some time. The Friedman test usually becomes negative when the serum prolactin has fallen to 50 M.U. or lower.

Smith and Smith<sup>19</sup> have suggested that hormone studies may prove of value in distinguishing true toxemias from "nephritic conditions" complicating pregnancy since in two nephritic patients in their group the serum prolactin was normal. Our observations would indicate that although nephritis itself apparently does not influence serum prolactin concentration, this becomes raised before or coincident with the onset of toxic symptoms in these patients.

*Pernicious Nausea and Vomiting.*—Thus far we have had the opportunity of studying only one such patient. E. K., aged 25 years, gravida i, was admitted to the ward at the fourth lunar month because of marked vomiting, a loss of weight of five pounds during the gestation, slight jaundice and acetoneuria. In contrast to the late toxemias of pregnancy, the serum prolactin was below the normal range for the period of gestation (80 M.U.) while the serum estrogen was normal (100 M.U. per 100 c.c.). This patient improved rapidly under therapy and the serum prolactin two weeks later had risen to 180 M.U. per 100 c.c.

On the other hand the Smiths<sup>19</sup> have suggested that nausea and vomiting is associated with low serum estrogen values, since in five cases of nausea and vomiting

Smith and Smith<sup>19</sup> have presented excellent quantitative studies on a small group of normal patients and a larger group of toxemic patients which demonstrated that the late toxemias of pregnancy are regularly associated with high values for prolactin and somewhat depressed values for estrogen. A number of similar reports on smaller groups of cases have also appeared in the foreign literature.

Our studies in a group of 22 patients with toxemias of late pregnancy (Figs. 3 and 4) also indicate high prolactin and low estrogen values. All of this group complained of symptoms of toxemia, had elevated blood pressures, and showed varying degrees of albuminuria. Sixteen were classified clinically as having pre-eclamptic toxemias and 6 as belonging to the group of "low reserve kidney."

Serum titrations made at the time these patients were admitted to the ward for treatment showed abnormally high prolactin values in 19 instances and abnormally low estrogen values in 17 instances. Both prolactin and estrogen deviated from the normal in 16 patients. In two instances of apparently mild pre-eclamptic toxemia, the prolactin and estrogen values were within normal range. In a third instance, the prolactin was within the normal range, and the estrogen was depressed, while normal estrogen and elevated prolactin values occurred in three instances. In one of the latter the estrogen was unusually high (1,000 M.U. per 100 c.c.).

For the group at large the severity of the toxemia of pregnancy has not shown any distinct relationship to the amount of deviation in prolactin and estrogen values, except that in following the individual cases there was in the majority of instances a fall in serum prolactin and a rise in the serum estrogen as the patient improved, while a wider deviation marked relapses. This reciprocal rise and fall in prolactin and estrogen, which has been commented upon by Smith and Smith,<sup>19</sup> was rather impressive by its consistency.

It was of interest that the patient with the highest rise in serum prolactin (Case 22, 1,800 M.U. per 100 c.c.) was admitted primarily because of marked edema of the extremities and face. This observation may prove to be of significance since two other patients in this group with more than the average amount of edema showed high prolactin values (Cases 8 and 13).

Premature separation of the placenta occurred in a patient of this group (Case 17) who had a late onset of pre-eclamptic toxemia. Blood taken at the time of cesarean section showed the serum prolactin to be elevated to 1,000 M.U. per 100 c.c. while the serum estrogen was unusually low, 66 M.U. per 100 c.c.

Of special interest were three additional patients originally in the group studied for normal values who developed toxemias in the latter months of pregnancy, and in whom a number of titrations were available before the onset of symptoms (Table I).

TABLE I. STUDIES ON THREE PATIENTS WHO DEVELOPED LATE TOXEMIAS

PATIENT	WEEKS	SERUM PROLACTIN	SERUM ESTROGEN	CLINICAL OBSERVATIONS
A. D.	16	800	50	Normal pregnancy
	20	330	100	
	25	200	100	
	28	330	250	
	31	330	400*	
	34	500*	330	Pre-eclamptic toxemia In ward, improved
	37	500*	100†	
	39	600*	400	
J. G.	25	200	120	Normal pregnancy
	29	250	300	
	33	200	200	
	37	1000*	180†	Pre-eclamptic toxemia In ward, improved
	39	500*	120†	
I. L.	20	160	80	Threatened abortion Bleeding and pains stopped
	21	330	100	
	23	330	120	
	27	500*	80	Impending toxemia? Pre-eclamptic toxemia In ward, improved
	32	660*	80†	
	35	800*	120†	
	37	500	330	

\*Represents values above normal range.

†Represents values below normal range.

## SUMMARY

I. A technique is described for the biologic titration of estrogenic and gonadotropic hormones in the serum of pregnant women which requires from 20 to 50 c.c. of blood.

a. Estrogenic hormone was assayed by a modification of the Fluhmann technique.

b. Gonadotropic hormone was titrated by a modification of the Asehheim-Zondek test.

c. Whole sera were used as the test solutions and mice as the test animals.

II. The estrogen and prolan values on unextracted sera are much higher than those obtained on extracted specimens.

III. Serum titrations repeated at frequent intervals gave much more consistent results than those obtained from urinary assays.

IV. A total of 162 serum titrations were conducted on 40 normal pregnant women in various periods of gestations, and graphs were prepared showing the normal range and average values from the fourth weeks of gestation to term.

V. Serum titrations conducted on a group of 22 patients with toxemias of late pregnancy usually showed abnormally high prolan and low estrogen values. The severity of the toxemia did not appear to be directly related to the degree of abnormality in prolan and estrogen values, except that those patients with marked edema showed unusually high serum prolan readings. Improvement in the clinical condition was generally associated with a return of the estrogen and prolan values to the normal range.

VI. Studies on three patients in whom titrations were available before the onset of toxemia showed in two instances high prolan values preceding the onset of toxemia by several weeks. These were later followed by low estrogen values.

VII. There was generally a reciprocal relationship between the rise and fall of estrogen and prolan.

VIII. Three patients with nephritic toxemia showed high prolan and usually low estrogen values during the period of clinical toxemia. However one patient with glomerulonephritis, who had a history of nephritic toxemia and eclampsia in the previous pregnancy, showed normal values for estrogen and prolan, except during two periods associated with signs and symptoms of toxemia.

IX. Where intrauterine fetal death was suspected repeated serum prolan studies furnished a better means of determining the fate of the fetus than did the Friedman test.

With our technique when the serum prolan fell to 50 M.U. per 100 c.c. or less the Friedman test usually became negative.

X. One patient with pernicious nausea and vomiting had a low serum prolan determination while the serum estrogen was normal.

The excellent studies of Taylor and Scadron also dealing with the concentration of the sex hormones in the late toxemias of pregnancy have appeared (*AM. J. OBST. & GYNEC.* 37: 963, 1939) since this paper was submitted for publication.

I am indebted to Dr. Norris W. Vaux for numerous helpful suggestions and facilities which made this study possible.

they found low levels of estrin in four and noted a marked rise accompanied by the cessation of these symptoms in all five. It is apparent that further studies on such patients are required.

It may be noted from these studies that the rather constant range of gonadotropic hormone in the latter half of pregnancy renders its routine determination in patients with toxemias of pregnancy more convenient and perhaps more reliable than estrogen values. Furthermore the prolan values can be obtained more quickly and conveniently since histologic preparations are rarely required, nor is it necessary to have castrated animals on hand. With our present technique we regard positive Aschheim-Zondek reactions obtained with quantities of sera less than 0.25 c.c. as being distinctly abnormal in the latter half of pregnancy. Furthermore, since the prolan values were somewhat more closely associated with evidence of toxemia than were the estrogen determinations, it would appear that the endocrine changes can in most instances be followed as readily from serum prolan determinations alone.

The association of an endocrine dyscrasia with the toxemias of pregnancy suggests that the former may be of etiologic significance. However, it is apparent that until we become better informed as to the sources of the sex hormones during pregnancy, and the mechanism which regulates their characteristic rise and fall, the ultimate source of any dysfunction will remain obscure. The influence of estrogenic and gonadotropic hormones on progesterone, and vice versa as well as their effect on many other hormones, also requires investigation.

It is to be noted that the high concentration of prolan per se can hardly be cited as the cause for the manifestations of toxemia, since even higher concentrations normally occur in the early weeks of gestation, while it might be further observed that in early pregnancy the estrogen values are even lower than those associated with toxemia.

#### CONCLUSIONS

It has been demonstrated that biologic assays for serum estrogen and prolan in pregnancy may be conducted with from 20 to 50 c.c. of blood by a technique which is not only simpler but considerably more accurate than the usual extraction methods. Although there is a considerable deviation of estrogen and prolan values in the various periods of normal gestation, these generally fall within a given range.

In the toxemias of late pregnancy the serum prolan values are usually high for the period of gestation, while the estrogen values are below the normal range. The degree of abnormality in these values does not appear to be related to the severity of the toxemia, nor to any one clinical symptom, except, perhaps, to degree of edema. The onset of toxemia appears to be preceded by a rise in serum prolan, and later by a fall in serum estrogen, while improvement in the clinical condition is followed by a return of these values to the normal range.

Nephritis complicating pregnancy does not appear to be associated with abnormal serum estrogen and prolan values, except when accompanied by toxemia. In nephritic toxemia the serum prolan was elevated and the serum estrogen lowered.

Pernicious nausea and vomiting in one patient was associated with a low prolan and normal estrogen determination, indicating that the endocrine dysfunction differs in the early and late toxemias of pregnancy.

Repeated serum prolan values are of aid in determining the fate of the pregnancy where death of the fetus is suspected.



DR. RAKOFF (closing).—Strictly speaking, the method of biologic assay for estrogenic hormone employed in this study is not a modification of Fluhmann's method in that vaginal cornification is the end point sought. However, where a number of ascending dosages of serum are used, mucification is the first evidence of estrogenic activity, and was regularly sought for as a point from which higher dosages were calculated. These showed further degrees of hyperplasia to the point of cornification. Even larger dosages were recognized by the production of uterine estrus, so that a number of methods must be combined to reach an end point with the least waste of serum and of animals.

As to the question concerning the presence of free and combined estrogenic substances, this was determined only in those instances in which urinary assays were made, the total estrogenic material being determined by the usual method of acid hydrolysis. In the serum titrations only the estrogenic activity of the whole unextracted serum was determined, since in our experience any type of extraction or hydrolysis lowered the total estrogen content.

As to the concentration of estrogenic hormone in patients with abortion, our experience thus far has been that prolactin concentration falls first, and is then followed by a diminution in estrogen. We feel that the prolactin values are more valuable in the prognostication of intrauterine fetal death.

Although we have not had the opportunity of studying the serum values in hydatidiform mole, two patients with chorionic tumors of the testicle with metastases were studied. In one the serum prolactin was much higher than is obtained in normal pregnancy; in the other the increase was not very much. Indeed in the latter case the Friedman test was negative.

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## THE GROWTH OF FETUS AND INFANT AS RELATED TO MINERAL INTAKE DURING PREGNANCY

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THE prevalent idea that the maternal organism can, independent of the diet, supply from her tissues a mineral nutriment optimum for the developing fetus needs to be qualified. It appears to be one of the many statements handed down in medical literature which is difficult to disprove because of the lack of sufficient experimental data. Apparently, the human organism has a wide range of adaptability, and the partial insufficiency of one or more minerals supplied to the fetus may not produce any visible clinical signs in the young infant. The optimum development, however, may have been interfered with, and deviations from the normal seen during the early postnatal period may be the direct effect of congenital conditions. It is the purpose of this paper to summarize what is known about fetal mineral content and to show from experimental and clinical sources what positive relationships exist between the growth of the offspring and the mineral intake during pregnancy.

To date, published data on the chemical composition on some 120 fetuses are available. Excellent and comprehensive summaries on mineral retentions of the fetus have been made by Coons and coworkers and by Macy and Hunscher.<sup>2</sup> Supplementary studies have been published recently dealing with the composition of fetal bone<sup>3</sup> and fetal iron.<sup>4</sup> This paper would become too long and unwieldy if all the known mineral elements of body composition were to be discussed. Therefore, it seems

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## DISCUSSION

DR. NORRIS VAUX.—This work is going to be of great value to us in the toxemias and in the matter of miscarriages and early abortions. Dr. Rakoff's work has pointed out that there is usually a definite endocrinologic cause for these interruptions of pregnancy, and also that we can prognosticate a possible oncoming toxemia. His work has added a modification to technical methods in that it has shortened the rather tedious histologic technique and avoided the extraction of the twenty-four-hour urine specimen. While the estimation of prolactin and the estrogens were run on the serum, urinary assays were undertaken as controls and, as Dr. Rakoff told you, he found the newer method much less expensive, as well as a great saver of time. In using smaller animals, much less blood from the patients is required.

The greatest importance of this work is that endocrinology has been further applied in a clinical manner to obstetrics. A normal range of rise of prolactin in the early months with later a gradual fall has been demonstrated. With the formation of the placenta there is a beginning estrogen rise. If in the early months of pregnancy the estimation of prolactin is low, there is something wrong, and we can prognosticate an early abortion or miscarriage. If estrogen readings are low in the latter months then these patients will show early toxemia. In a few instances where nephritic toxemia was present, these low readings were also found to be present.

DR. CHARLES MAZER.—I want to call attention to the fact that the test described is not a modification of the Fluhmann test for estrogenic substance. Fluhmann employs mucification of the vaginal mucosa of the rodent as a criteria of estrogenic activity. That permits detection of smaller quantities of estrogen than the Allen-Doisy test, which Dr. Rakoff is employing. It is immaterial whether the final result is ascertained by microscopic examination of the vaginal mucosa or by the vaginal smear method.

The advantage of determining simultaneously, the amount of estrogen excreted in the urine is mainly in the fact that both the quantity of active and combined estrogens can thus be determined, whereas in blood studies the quantity of active estrogens is determinable.

DR. FRANKLIN L. PAYNE.—The establishment of normal values for the chorionic and estrogenic hormone in the blood serum and urine during the various stages of pregnancy will prove to be immensely useful to the clinician. By quantitative serum studies he was able to diagnose intrauterine fetal death. Frank has stated that this fetal death is accompanied by a precipitous drop in the estrin contents of the blood. It would be interesting and of clinical value to learn which of these substances decrease first. Of equal importance is the application of these normal figures in the hormone diagnosis of hydatidiform mole and chorioepithelioma. While neither of these conditions is always attended by characteristic hormone values in the blood or urine, it is by contrasting such values with the normal concentrations that diagnosis may be facilitated.

weight and length of the fetus which determine fetal age. It will be shown by the growth graphs for nitrogen, calcium, phosphorus, and iron that if curves were constructed from earlier data<sup>1</sup> slight variations would appear when these figures are compared with results from more recent determinations.<sup>5</sup> The differences may be due principally to three factors, (1) analytical methods, (2) variation in body composition, and (3) the difficulty in obtaining exact body measurements. The last factor becomes very important in any calculation where absolute increase in weight is plotted against time.

In Fig. 1 are shown the curves for nitrogen, calcium, phosphorus, and iron. Some slight discrepancies between the two groups of data for nitrogen are to be noted before the eighth lunar month. It is suggested that the differences found here and in the two following curves, may be due to difficulties suggested in the preceding paragraph. Apparently nitrogen retention for the last two lunar months is 62 per cent of total body content of the term fetus.

For calcium the differences, although greater, are found during the same lunar months as for nitrogen. It will be seen from the curve that the calcium retained in the last two months is 65 per cent of the total body content of the term fetus.

The two groups of data obtained for phosphorus are in close agreement. About 64 per cent of the total phosphorus content of the term fetus is retained during the last two months of pregnancy.

The data for iron obtained from eighteen fetuses analyzed at various ages are compared with values published by Macy and Hunscher.<sup>2</sup> The curves are identical except for the term fetus. It appears from these data that the iron retention during the last two months of pregnancy is 67 per cent of the total fetal iron at term.

It may be said that these retention growth curves all exhibit a similar pattern. Further work will undoubtedly show that they do not represent the optimum mineral retentions, but the agreement found for values so far published would indicate that a working average has been obtained. Also, the smoothness and slope of the curves indicate that mineral increase during the fetal period is a steady continuous process.

In the early months of fetal life, as shown by the mineral curves, the nutritive demands upon the mother are small, and it would be reasonable to assume that fetal needs are readily supplied. Contrary to this assumption are the findings of Schmitz<sup>6</sup> who, after the World War, found consistently lower figures for calcium content of young fetuses from undernourished mothers. Confirmation of these figures would be of practical importance, since it would indicate that a poorly nourished mother who is on a starvation diet may be unable to supply the fetus even in the early months. If the fetus must depend on decalcification of the mother's skeleton or on her low iron stores, it would appear that in this respect gestation takes on a pathologic aspect.

#### THE MINERAL METABOLISM OF THE RAT

*Calcium and Phosphorus.*—The following paragraphs barely touch upon the literature of this subject. The review is intended only to emphasize the findings of a few of the more recent studies.

advisable to consider in more detail only the retentions of nitrogen, calcium, phosphorus, and iron.

It may be assumed: (1) that the average nutritional requirements of the fetus with respect to nitrogen, calcium, phosphorus, and iron are shown by the analyses of the fetal composition; and (2) that such analyses show the variations in composition during any period of fetal growth.

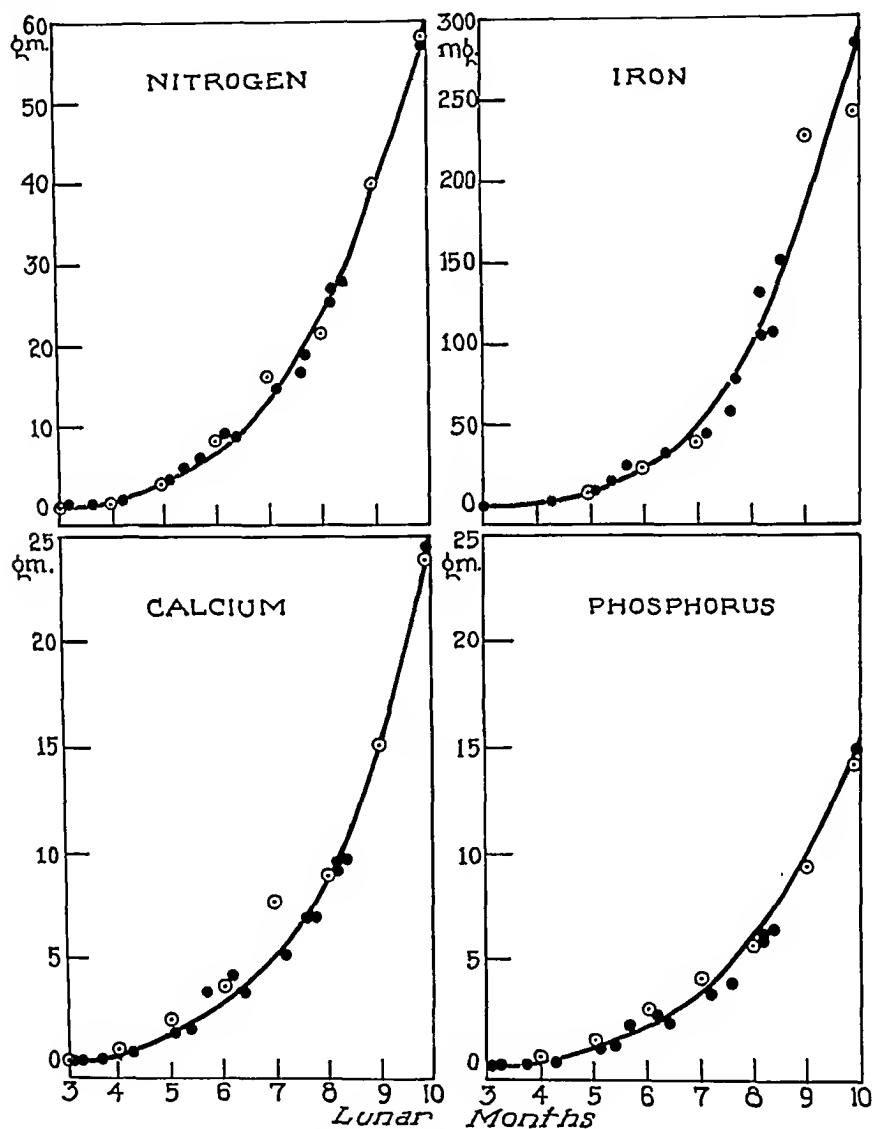


Fig. 1.—Shows the content of nitrogen, calcium, phosphorus, and iron of the fetus from the third to the end of the tenth lunar month. In all of the curves the author's data are represented by the solid dot.

The material analyzed in an investigation of this type deserves some consideration. In most instances some adverse condition is responsible for the interruption of pregnancy or the early death of the premature infant. Apparently, the material analyzed must be chosen with much care since dehydration and starvation change the measurements of

one which was microeytic in type. They further showed that if the iron deficient diet was continued over the period of two pregnancies, the second litter was reared with difficulty, the pups were of subnormal weight and had an even more pronounced anemia than the first litter. Alt<sup>12</sup> has confirmed this work by chemical determination of the iron content of the liver of rats and the total iron content of the offspring. He showed that a diet low in iron caused a marked depletion of the iron in the liver of the mother rat. He showed further that the first litter from rats on a diet low in iron had only one-half the normal iron content and three-fourths of the normal hemoglobin. The second litter from these same rats on continued low iron diet had only one-fourth the normal iron content and one-half the normal hemoglobin value.

The conclusions apparent from the animal studies cannot be used to prove that the same results occur in man, but only to suggest that the same general biologic processes may exist.

#### THE MINERAL METABOLISM OF MOTHER, FETUS AND INFANT

*Calcium and Phosphorus.*—No parallel studies are possible for the human being comparable to the experiments briefly mentioned. There are, however, isolated facts and clinical observations which collectively indicate the interdependence of the mother's diet and fetal growth.

The balance experiments on two groups of pregnant women by Coons and others<sup>1</sup> made in widely separated localities (Chicago and Oklahoma) represent the most comprehensive investigations of this kind. A comparative study of the results obtained on these two groups show some interesting values for the retentions of calcium, phosphorus, and iron. For the group in Oklahoma both calcium and phosphorus retentions were much higher than in Chicago. However, the highest retentions of phosphorus were considered insufficient for proper skeletal and soft tissue growth of the fetus. The better retentions by the southern group were not thought to be due to differences in the diets but rather to the greater amount and intensity of the antirachitic activity of southern sunshine. It is interesting to note also that the Ca:P ratios of the diets were approximately 1:1 whereas the ratios of the amounts retained, of these two minerals, varied from 0.23 to 3.07. This observation illustrates the selective tendency of the organism irrespective of dietary composition. With respect to iron retentions the groups were reversed. Twice as much iron was retained by the northern women. Apparently the iron content of the diets for the two groups was approximately the same. Of interest also are the few comparisons of growth and development of the infants born to the two groups of mothers. Considering only

TABLE I. THE CALCIUM AND PHOSPHORUS OF THE HUMAN FETUS IN GRAMS PER KILOGRAM OF DRY, FAT-FREE SUBSTANCE

FETUS	AGE LUNAR MONTHS	CALCIUM GM.	PHOSPHORUS GM.
14	3.0	17.6	17.0
13	3.2	32.0	22.5
12	3.7	27.1	24.0
17	4.3	29.9	20.1
15	5.1	41.2	29.1
9	5.4	40.7	28.4
6	5.7	57.4	35.9
5	6.2	49.3	30.9
8	6.4	42.7	29.0
11	7.2	40.3	27.7
1	7.6	48.2	28.8
10	7.7	40.3	27.1
2	8.2	38.6	26.0
4	8.2	40.7	28.0
3	8.4	39.4	26.9
7	10.0	46.9	28.8

In 1930 we found that newborn rat pups of equal weight differed considerably in their calcium and phosphorus content. This finding suggested a further investigation to determine if changes in the diet of the pregnant rat could noticeably affect the mineralization of the offspring. A preliminary report of this work was published in 1932. It showed that even on an adequate diet the addition of vitamin D caused an increase in the calcium and phosphorus contents of the rat pup. In the same year Nicholas and Kuhn<sup>8</sup> showed that when 0.5 c.c. of viosterol was given daily to pregnant rats on a basic diet the offspring had a slightly higher calcium content than that of young born of control rats; and that when the basic diet was deficient in minerals and vitamin D, the calcium content was less than for the controls. The phosphorus content, however, was approximately the same as that of the controls with either type of diet. In 1935 we published a statistical report<sup>9</sup> on the mineral analyses of several hundred rat pups. In the first three columns, Group A of Fig. 2, are shown graphically the results of that study. The basic diet plus vitamin D as viosterol or as found in cod liver oil increases the body content of both calcium and phosphorus. In 1936 Sontag, Munson and Elton<sup>10</sup> attacked other aspects of this

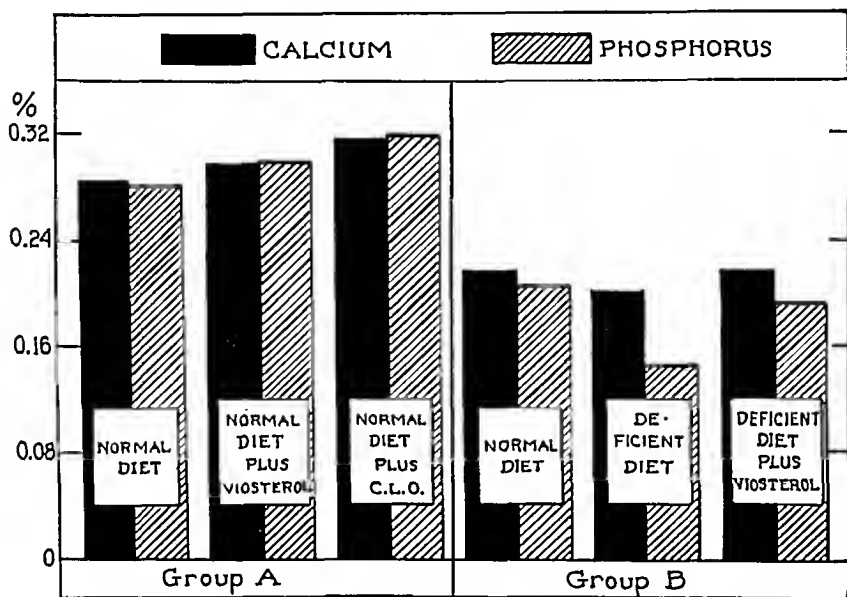


Fig. 2—Illustrates the effect of changes in the diet of the pregnant rat on the calcium and phosphorus content of the offspring.

problem. They showed, as graphically illustrated by the last three columns, Group B, in Fig. 2, that pregnant rats on a diet deficient in calcium and phosphorus gave birth to offspring having a lower calcium and phosphorus content than the control rats on an adequate diet; and that therapeutic doses of vitamin D given to pregnant rats on this deficient mineral diet increased the calcium content to normal value but the phosphorus content, though raised, remained below the normal level.

These studies show that the diet of the pregnant rat when fortified by vitamin D can affect the calcium and phosphorus content of the offspring as follows: (1) If the diet is low in the required minerals the body content approaches the normal level; and (2) if the diet is sufficient the normal level is exceeded. Sontag and coworkers<sup>10</sup> concluded from their study that "abnormalities of vitamin D content of the diet of pregnant rats have much the same effect on the offspring of these rats as such a diet would have if administered directly to young rats. The experiment indicates that fetal mineralization is not independent of the mineral metabolism of the rat mother."

*Iron.*—Parsons, Hickmans and Finch<sup>11</sup> have shown by study of the blood during the lactation period that iron deficient diets of the pregnant rat produced an anemia in the offspring more marked than the usual physiologic anemia of rat pups and

sequently, the new body substance and particularly the bone formed must be poorer in calcium and phosphorus. Apparently then the growing bones are in a state of continuous change and the minerals of the skeleton in a labile state permit growth of bone until the mineral retentions from the food become adequate. The early development of rickets, more often in the premature than the term infant, depends upon at least three factors: (1) the mineral content of the fetal skeleton; (2) the rapidity of skeletal growth; and (3) the length of time necessary for adequate calcium and phosphorus retentions. According to Hamilton<sup>15</sup> calcium retentions in premature infants are very low from the first to the fifth month. This fact and the greater growth urge predispose the premature infant more certainly to rickets.

At the present time rickets furnishes the best evidence of the interdependence of fetal and infantile skeletal growth and the mother's diet. Coons<sup>1</sup> and others suggest that the low calcium content of fetuses reported by Schmitz<sup>6</sup> soon after the World War was due chiefly to the undernourished condition of mothers. In 1926 Greenebaum and coworkers<sup>16</sup> reported the incidence of rickets in two groups, each containing 25 infants. A comparative study showed that the occurrence and degree of rickets were markedly less in the group where the maternal diets were made adequate. They concluded that "if the diet of the mother during the last three months of pregnancy can be made approximately correct in caloric and mineral intake, while it will not prevent rickets, it will have a controlling influence on the development of the disease in her offspring."<sup>11</sup>

TABLE II. FETAL IRON

FETUS WEIGHT GM.	BODY CONTENT		FETUS WEIGHT GM.	LIVER CONTENT	
	FAT-FREE DRY SUBSTANCE MG. PER KG.	TOTAL PER FETUS MG.		DRY SUB- STANCE MG. PER KG.	TOTAL PER LIVER MG.
14	712	0.7	162	1333	1.7
115	469	6.0	530	1183	6.7
259	300	10.6	750	1980	18.4
335	398	17.2	770	1242	11.0
490	378	24.0	819	1667	11.2
570	384	32.0	860	2470	18.7
1010	433	48.8	860	1130	7.9
960	359	59.2	900	3454	32.2
1205	413	80.6	1295	2470	29.6
1555	355	105.6	1540	3055	44.8
1545	491	134.4	1750	1070	15.4
1615	416	111.0	2670	3160	72.3
2250	400	152.3	2950	3474	117.9
2915	454	284.2	4030	2339	118.5

The most conclusive evidence of inadequate fetal nutrition is the reported cases of congenital rickets and those early cases where insufficient time since birth had elapsed for rickets to develop. Maxwell and others<sup>17</sup> have reported 2 cases in newborn Chinese infants, Dunham<sup>18</sup> has reported 1 case (patient thirty-four days old), and Eliot and Park<sup>19</sup> have reported 8 cases of early rickets in infants two weeks to one month old, diagnosed at autopsy. Rachitic changes have also been noted by Ylppö<sup>20</sup> in newborn premature infants to the extent of 5 per cent. Hess<sup>21</sup> has also occasionally noted on x-ray plates "epiphyses of newborn infants which instead of being sharp are slightly frayed with a tendency to cupping, such as might be termed incipient rickets in later months."

*Iron.*—The literature on the interdependence of the maternal and the fetal and the infant iron metabolism is more controversial than that of the two minerals discussed. Only very short references will be made to the more important observations bearing on the subject.

In Table II, data are reported on 28 fetuses,<sup>4</sup> 14 for the total body iron and 14 for the content of liver iron. The iron content per kilogram of fat-free dry substance remains practically unchanged during the fetal growth period, but the liver

averages for these two groups, the southern infants weighed a pound more at birth, their teeth erupted earlier and more rapidly, and the infants were advanced in muscular development as shown by lifting of head, sitting, standing and walking.

Much attention has been given to the question of mineral storage of calcium, phosphorus, and iron during the last months of fetal life. While some earlier analyses of the fetus seemed to show that the calcium and the phosphorus content increased faster near term than the solid body substance, recent investigations failed to confirm this conclusion. If a comparison is made of Langstein and Edelstein's<sup>13</sup> figures for calcium and phosphorus content per kilogram of fat-free body substance with those of Camerer and Söldner,<sup>14</sup> the amounts of these minerals for a seven months' and a full-term fetus are about the same. In Table I the absolute amount

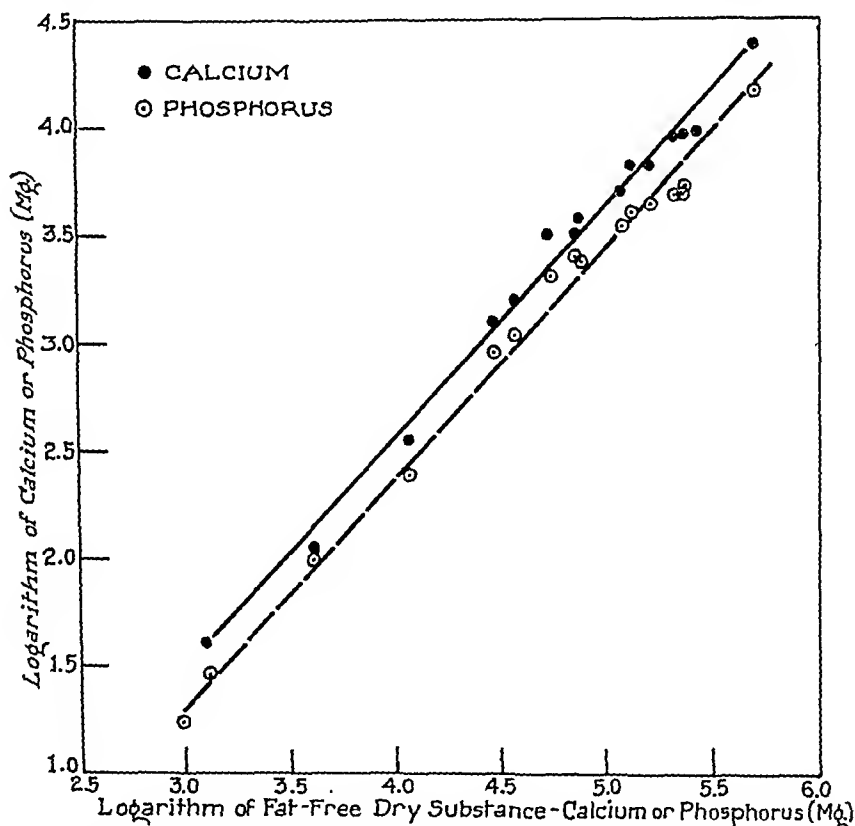


Fig. 3.—Illustrates the relationship between the calcium or the phosphorus content to the fat-free dry body substance (minus the calcium or the phosphorus) of fetuses from the third to the end of the tenth lunar month.

of calcium and phosphorus per kilogram of dry fat-free body substance does not change materially from the fifth to the tenth lunar month. In Fig. 3, the logarithms of the absolute values of calcium and phosphorus plotted against the logarithms of the dry fat-free body substance for each month from the third to the tenth lunar month give parallel and straight lines. This evidence demonstrates that no relative increase of calcium and phosphorus occurs in the last months of gestation. Apparently storage in the strict sense of the word does not take place, but what does occur is an attempt on the part of the fetus to secure optimal mineralization of its skeleton.

During the period of early infancy balance experiments indicate that the calcium and phosphorus retentions are much lower than in the last weeks of fetal life. Since the average birth weight increases 100 per cent in the first five months, the skeleton, approximately the same proportional part of the body, must also grow rapidly. Con-



Several recent publications have stressed the relationship existing between the iron deficiency during pregnancy and the hypochromic anemia that appears before the sixth month of life. This anemia of infancy when not affected by some associated disease is not due to congenital abnormal blood formation since these infants have normal blood at birth.<sup>32</sup> Furthermore, postnatal nutrition of all infants during the first four months is much the same because the food is restricted to milk and vitamin supplements.

In 1931 Maekay<sup>33</sup> published a comprehensive study on nutritional anemia in infancy, in which a comparative study was made between infants born to moderately anemic mothers (54 to 70 per cent hemoglobin) and infants born to mothers with normal hemoglobin values. The infants born to the anemic mothers showed a lower hemoglobin level at every month for the first six months of life than did the infants born to the nonanemic mothers. From this study Maekay concludes that anemia of the mother predisposes the infant to anemia during the first year. A later paper by Neale and Hawksley<sup>34</sup> emphasizes the finding of anemia in twins born to anemic and nonanemic mothers. The demand upon the mother for iron in a twin pregnancy is considerably more than in single pregnancies and even though the mother's hemoglobin may be normal, all her stores may be consumed and one or both of the twins will develop anemia. Finally, the most conclusive study on this subject is that of Strauss<sup>32</sup> since it compares a series of 14 mothers with less than 45 per cent hemoglobin with a series of 12 mothers with hemoglobin over 70 per cent. Statistically there was no significant difference between the two groups of the hemoglobin values at birth. However, when these infants were examined one year later, it was found that the infants born to anemic mothers had an average hemoglobin value of 46 per cent as compared to 67 per cent for the infants born to nonanemic mothers. Strauss suggests the data "indicates that infants born to mothers suffering from iron deficiency although exhibiting at birth a normal blood picture, are unable to maintain a normal hemoglobin level during the first year of life." These investigations demonstrate that maternal iron storage during the period of pregnancy is at fault, since this hypochromic anemia of the infant may be prevented either by iron administered to the mother during pregnancy or by early administration of iron to the infant.

#### COMMENT

The object of this résumé on the interdependence of the fetal growth and the maternal diet is to emphasize the need for better mineral retention of the offspring. The prevention of rickets should not be used as the only criterion of the vitamin D requirement. According to Jeans and Stearns,<sup>35</sup> "It is at least reasonable to think that the optimum amount of any nutritional essential is somewhat greater than the amount which barely prevents clinical pathological changes." If then, the optimum mineralization of the fetus were more widely known and attempts made to reach this level, freedom from rickets, good growth and development could be assured in early infancy.

The same general relationship holds for iron stores and anemia. If the hemoglobin and iron storage in the liver are high at birth, all other things being equal, the infant stands a better chance of not developing hypochromic anemia during the first year.

It is admitted that treatment of both rickets and anemia may be started in early infancy. However, prophylaxis is more rational and adds a factor of safety. Toverud<sup>22</sup> suggests that "we pediatricians have to feel that our prophylactic work will be more consequent and give better results if we might be able to feed the infant not only from the moment of birth but from the moment of conception."

iron similarly calculated increases in the term fetus. The analyses here summarized, however, do not differentiate between hemoglobin and nonhemoglobin iron of the liver. The figures demonstrate only that even though the liver becomes somewhat less vascular, the iron increases. These results were obtained of fetuses born to women having normal hemoglobin values. The only quantitative studies pertaining to the iron content of the livers of newborn infants born to anemic mothers were made by Toverud.<sup>22</sup> She found a slight decrease in the nonhemoglobin iron content in 8 of 12 infants dying shortly after birth. The values found in the literature for nonhemoglobin iron content of the liver appear to be about 50 per cent of the total liver iron, from 50<sup>23</sup> to 60<sup>22</sup> mg. The importance of this iron store in the liver will become apparent when a comparison is made with other sources of iron.

In recent studies on the blood of newborn infants, the suggestion has been made that the iron obtained from the so-called excess hemoglobin at birth is two to three times the estimated nonhemoglobin iron in the liver. This suggestion, if correct, would minimize the significance of the iron store in the liver. However, calculations based on recent figures for total iron of the body, and hemoglobin values obtained at birth on the cord blood, show that the store of iron in the liver appears to be as large as that from any other source.

In 1937 Fullerton<sup>24</sup> by approximate estimations for iron in the various body tissues at birth calculated the iron content of the newborn infant to be 450 mg. This value is much too high since actual iron determinations on the term fetus give an average figure of 280 mg.<sup>3, 25</sup> Further, the normal newborn infant has a cord-blood hemoglobin value of 16.8 gm.<sup>26</sup> per 100 c.c. This figure drops to 11 gm.<sup>27</sup> per 100 c.c. at the end of two months. Even with the greater blood volume\* at the end of the second month the amount of hemoglobin in the circulating blood is 18 gm. less. The decrease of this blood constituent represents the excess hemoglobin from which 60 mg.† of iron may be liberated and stored in the body. If either the mean of the values for the hemoglobin content of the cord blood as found by Guest, Brown and Wing<sup>29</sup> or the mean found one to five hours after birth by Kato and Emery,<sup>27</sup> about 18 gm. per 100 c.c., is taken as an average, the iron from the excess hemoglobin amounts to 80 mg. The difference between this figure and the 60 mg. of nonhemoglobin iron in the liver as 20 mg. This amount is of no significance since the assumed blood volume at birth, 14.7 per cent, may be too high,<sup>25</sup> and the amount of hemoglobin based on 18 gm. per 100 c.c. would contain 280 mg. of iron, the total body content. This is improbable since the nonhemoglobin iron in the full-term fetus is by conservative estimation 60 to 80 mg. Therefore, for all practical considerations, equal amounts of iron may be expected from the excess hemoglobin and from the liver stores.

The importance of the iron stores for the formation of new hemoglobin may be considered. In a normal two months' old infant with 11 gm. of hemoglobin per 100 c.c., approximately 60 gm. of hemoglobin containing 200 mg. of iron, would be in the circulating blood. If, according to Stearns and McKinley,<sup>30</sup> the iron loss of the infant on a cow's milk diet averages from 50 to 75 mg. during the first two months of life, then the hemoglobin iron and iron loss would approximately account for all the iron present at birth. This would either leave the iron body stores completely exhausted or more likely result in the early appearance of anemia. On breast milk feeding, however, the infant is more often in a state of positive, though slight, iron balance as contrasted with the usual negative balance found on cow's milk feeding. It is, therefore, in this latter condition that high iron stores of the liver protect the infant from the hypochromic type of anemia. While the liver store of iron and hemoglobin concentration at birth and the kind of feeding are of importance in the consideration of anemia in early infancy some other factors as: (1) the rapidity of growth, (2) the number and severity of infections, and (3) the use of iron salts in the diet must also be taken into account.

\*Blood volume at birth is about 470 c.c., 14.7 per cent of body weight. At two months the blood volume is 550 c.c., 10.9 per cent of body weight (Lucas and Dearing.<sup>28</sup>

†3.35 mg. of iron per gm. of hemoglobin was used to calculate hemoglobin iron (Butterfield<sup>31</sup>).

## THE EVALUATION OF THE HUMAN VAGINAL SMEAR IN RELATIONSHIP TO THE HISTOLOGY OF THE VAGINAL MUCOSA

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**I**N RECENT years, our understanding of the endocrine factors involved in a number of gynecologic conditions has been dependent, in a great measure, upon the development of methods of estimating the functional activity of the ovaries. The introduction of the vaginal smear technique by Stockard and Papanicolaou<sup>1</sup> in 1917 and its application by Allen and Doisy<sup>2</sup> as a quantitative method of assaying follicular hormone, have opened up new opportunities for workers in the field of endocrinology. In the human being, the introduction of quantitative assay methods by Frank and others for the determination of estrogens in the blood and urine has yielded a great deal of information about some of the obscure problems in gynecologic endocrinology. These determinations, however, are time-consuming and costly and necessitate the collection of urine over a period of many days. Furthermore, it is not entirely clear at present how to interpret the estrogen excretion in relation to ovarian function. In our investigations of a group of cases in the out-patient department, we felt the need for a simple method of estimating ovarian function. Papanicolaou's<sup>3</sup> introduction of the vaginal smear technique in human beings seemed to offer a promising solution to the problem.

Papanicolaou<sup>3</sup> has described cyclical changes in the cytology of the human vaginal secretions corresponding to the follicle changes in the ovary. The changes described, however, are slight in degree and require a great deal of experience to interpret. Subsequently, Papanicolaou and Shorr<sup>4</sup> reported that after the menopause and after castration the human vaginal smear reveals striking cytologic characteristics which distinguish it from the smear obtained from women with normally functioning ovaries. They also demonstrated that the smears could be changed to resemble those of the normal cyclical women by the administration of an adequate amount of estrogenic hormone. This method of study of the vaginal secretions offered a simple, direct means of evaluating the estrogenic activity of the human ovaries and the efficacy of administered estrogenic substances. The Papanicolaou technique of preparing the smears we found to be too complicated and time-consuming to be practicable for a busy clinic. Salmon and Frank<sup>5</sup> have described a simplified method of preparing the vaginal smears which enables a reading to be obtained within a few minutes after the smear is taken. Because of the departure from the Papanicolaou technique, we felt it desirable to determine how reliably one can interpret the smears prepared by this method and how accurately they reflect the changes in the vaginal mucosa.

## SUMMARY AND CONCLUSIONS

1. Graphs are shown illustrating body content of nitrogen, calcium, phosphorus, and iron during the last seven lunar months.

2. Metabolism experiments on animals show that the diet of the mother enhanced by vitamin D will increase the transmission of calcium and phosphorus to rat pups. When diets insufficient in iron are given to mother rats a reduction of the iron content of rat pups by one-half will result, and, if diet is prolonged in the same female, the second litter will have only one-fourth the amount of body iron.

3. Metabolism experiments on comparative groups of pregnant women suggest that the vitamin D factor produced by sunlight plays an important part in their mineral retention. The occurrence of congenital and early rickets indicates that mothers may not provide the fetus with sufficient calcium and phosphorus for proper growth of the skeleton. Studies on iron indicate (1) that the normal full-term infant is born with a store of iron in the liver, (2) that this iron source is quite as important as the amount of iron which may be liberated from excess hemoglobin, and (3) that infants born to anemic mothers are subject to hypochromic anemia during the first year of life.

4. Experimental and clinical data, while incomplete in many respects, combine to demonstrate the importance of an adequate diet during the period of pregnancy to promote optimum growth of the fetus and young infant.

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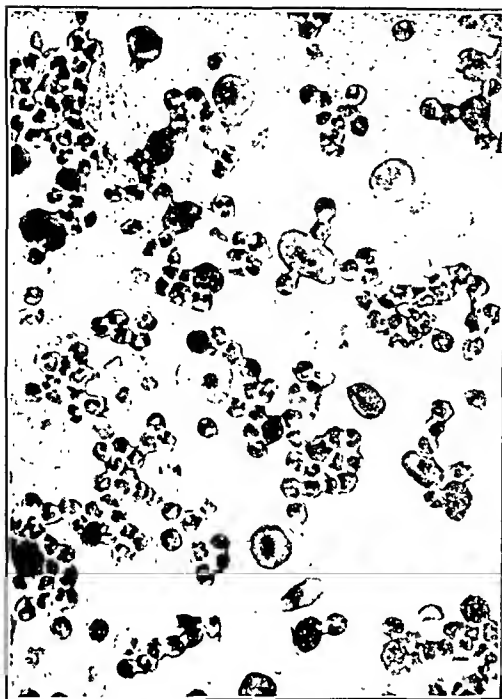


Fig. 1.



Fig. 2.

Fig. 1.—Reaction I. Advanced estrogen deficiency. Vaginal smear taken from patient B.L., aged 54, nine years after the menopause. The smear contains the typical "atrophy cells," leucocytes, and a few erythrocytes.

Fig. 2.—Reaction II. Moderate estrogen deficiency. Smear taken from patient S.B., aged 48, four years after bilateral ovariectomy. Note presence of moderate-sized epithelial cells as well as "atrophy cells," leucocytes, and erythrocytes.

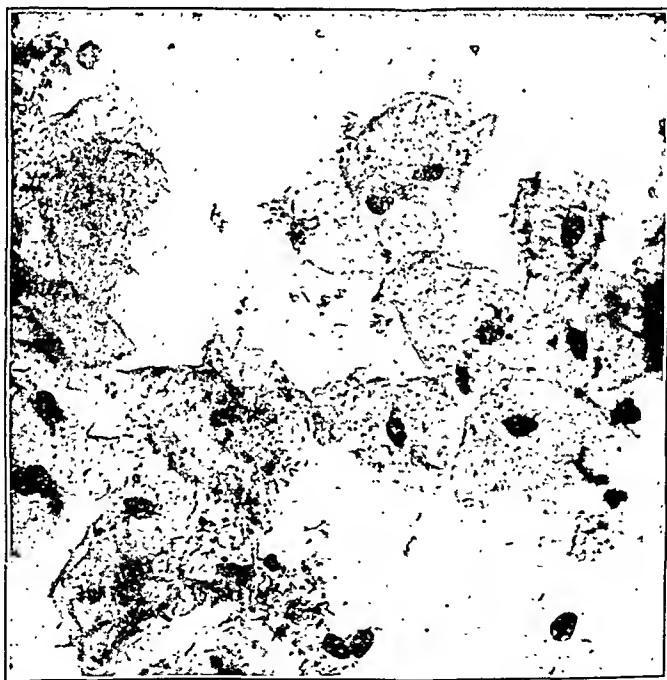


Fig. 3.—Reaction III. Smear taken from patient J.W., aged 43, ten months after spontaneous menopause. The epithelial cells are larger than in the Reaction II smear (Fig. 2). They vary in shape, are irregular in outline and have a tendency to form in clumps.

## EXPERIMENTAL PROCEDURE

A group of 60 women, who came to the clinic because of menopause symptoms, were selected. Preliminary vaginal smears were taken 3 times weekly for two weeks. At the end of this time, a vaginal biopsy was taken from the left fornix of the vagina. The patient was then given estrogenic hormone therapy either intramuscularly or by mouth. For the intramuscular injections, estradiol benzoate (progynon-B)\* in sesame oil was used. The oral preparation was dihydroxyestrin tablets (progynon-DH).† After the preliminary biopsy, estrogen therapy was begun immediately. Smears were then taken 3 times weekly and a biopsy taken from the left fornix of the vagina at the completion of the course of therapy.

## TECHNIQUE OF VAGINAL SMEAR STAIN

A speculum is inserted into the vagina and the vaginal mucous membrane and cervix inspected to exclude the presence of any infection. A small amount of the vaginal secretion is aspirated from the surface of the posterior blade of the speculum with a small glass pipette. The secretion is diluted with a little normal saline, spread on a glass slide, allowed to dry in the air and stained for one minute with fuchsin;‡ the smear is then washed with tap water and is ready for examination.

The biopsies were taken with an ordinary cervix biopsy punch. Of the 60 cases studied, 10 were x-ray castrates, 20 were spontaneous, and 30 were surgical castrates.

## VAGINAL SMEAR CLASSIFICATION

The smears were classified into 4 groups to indicate various degrees of estrogen deficiency.

*Reaction I.*—(Advanced estrogen deficiency.) The characteristic features of this type of smear are the complete absence of squamous epithelial cells and the presence of small, round or oval epithelial cells with rather large, darkly-staining nuclei ("atrophy cells"). These are the cells which Papanicolaou and Shorr have described as "deep cells." Leucocytes and erythrocytes are present in varying numbers (Fig. 1).

In some smears the epithelial cells are few in number and associated with large numbers of leucocytes; in others, particularly in very old women, the epithelial cells are very small, few in number and are associated with a scattering of leucocytes and erythrocytes.

*Reaction II.*—(Moderate degree of estrogen deficiency.) There is a variable number of large, epithelial cells many of which are irregular in shape. The nuclei are relatively large. Interspersed among these cells is a varying number of "atrophy cells" and leucocytes. The relative proportion of the large epithelial cells to the "atrophy cells" is variable. What distinguishes this smear from the I and the III is the association of the "atrophy cells" with the larger epithelial cells (Fig. 2).

*Reaction III.*—(Slight degree of estrogen deficiency.) Predominance of rather large irregular epithelial cells is the striking feature of this smear. The cells vary in size and shape, their edges are somewhat irregular and frequently indistinct in outline. They frequently occur in clumps; a few "atrophy cells" may be present (Fig. 3).

*Reaction IV.*—The smear consists of large, flat, clearly-outlined, squamous epithelial cells with small, deeply-staining nuclei. These cells are larger, more clear-cut and the nuclei relatively smaller than those in the III smear. No "atrophy cells" and usually no leucocytes are seen (Fig. 4).

*The Morphology of the Vaginal Mucosa after Cessation of Ovarian Activity.*—Of the vaginal biopsies taken from the 60 cases before treatment, all but one showed

\*For the progynon-B and progynon-DH used in this investigation, we are indebted to Drs. Stragennell, Schwenk, and Gilbert of the Schering Corporation, Bloomfield, N. J.

†Reagent: 1. Fuchsin 3.0  
Alcohol 95 to 100.0%  
2. Alcoholic fuchsin (1) 12.0  
Distilled water 100.0

is also a striking variation in the responsiveness of different individuals to the same amount of administered hormone. In some individuals 120,000 R.U. by mouth will evoke, as illustrated by Case 4, a marked regeneration of the vaginal epithelium with almost complete restoration to normal. In others the same dose produces only a very slight, patchy regeneration.

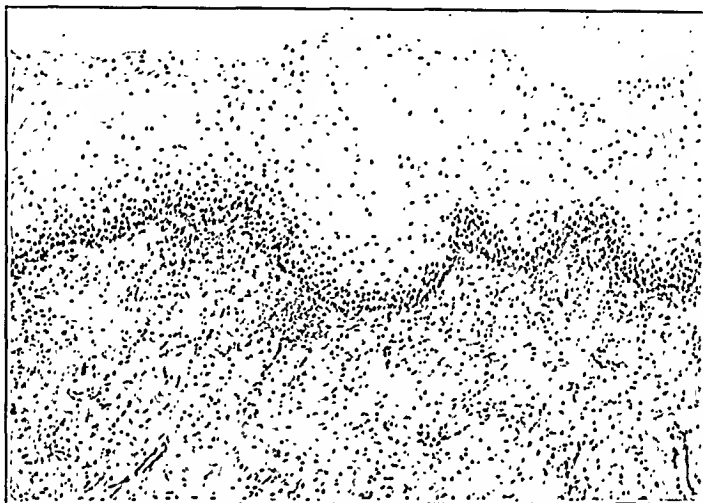


Fig. 9.—Vaginal mucosa of Case B.L., aged 54, nine years after spontaneous menopause. Biopsy taken after 120,000 R.U. estradiol (by mouth) in two weeks. Note regeneration of vaginal mucosa but absence of cornification. Compare with Fig. 5 (showing mucosa before treatment) and with Fig. 10, showing vaginal smear after treatment.

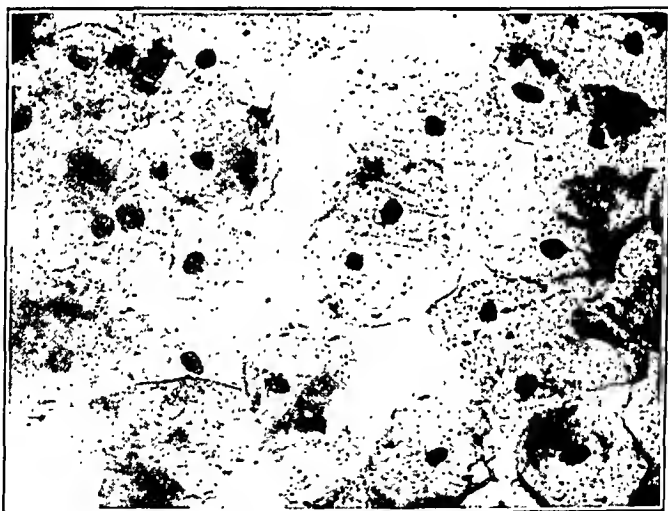


Fig. 10.—Vaginal smear taken from patient B.L., after 120,000 R.U. estradiol by mouth. Compare with pre-treatment smear (Fig. 1).

There is, furthermore, a qualitative variation in the character of the epithelial proliferation in different cases. In some cases the first evidence of reaction to the administered hormone is proliferation of the basal layer and the development of 2 or 3 layers of flattened epithelial cells on the surface without actual cornification. In others, there appears to be a rapid proliferation evidenced by the marked increase in thickness of the mucosa which may be 15 to 20 cell layers deep, as illustrated in Case 4 (Fig. 10). It is noteworthy, that the vaginal mucosa after estrogen treatment is not entirely restored to a normal status. It is also of interest that in none of the cases was there any evidence of abnormal epithelial proliferation.

some degree of atrophy of the mucous membrane. To facilitate classification, the different stages of atrophy were classified into 4 grades.

*Grade I:* (Most advanced degree of atrophy.) The mucosa consists of a thin layer of epithelial cells which vary in depth from 1 to 6 cell rows. In some areas the epithelium is completely absent. The normal differentiation into layers is lost. There are no papillae and no cornification layer. There are numerous areas of sub-epithelial round cell infiltration (Fig. 5).

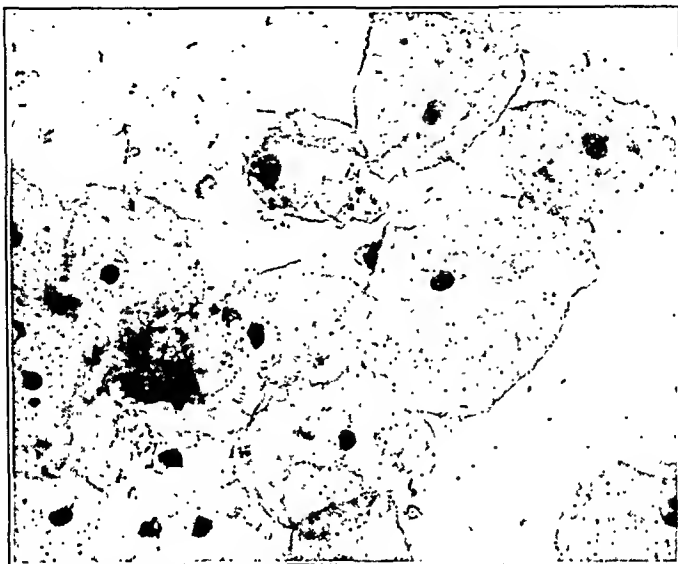


Fig. 4.—Reaction IV. The cells are large and flat; the edges clean cut; nuclei pyknotic. No "atrophy cells" are present. Smear taken on the eighteenth day of the cycle from young woman, aged 23, with a normal, regular menstrual cycle.

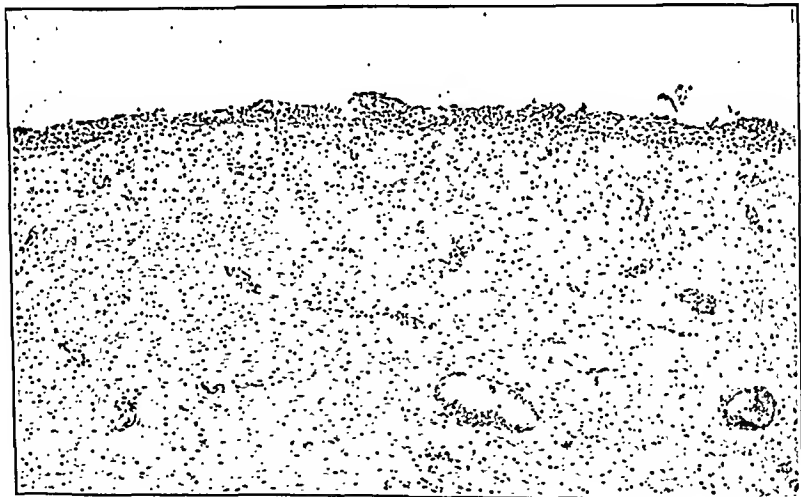


Fig. 5.—Grade I. Most advanced degree of atrophy. Case B.L., aged 54, nine years after the menopause. Note thinness of epithelial layer, absence of differentiation into zones, absence of papillae and cornification. Compare with smear shown in Fig. 1.

*Grade II:* (Moderate degree of atrophy.) The mucous membrane consists of a much thicker epithelial layer, varying in thickness from 4 to 10 cell rows. Differentiation into basalis and functionalis is present only in some areas and is not sharply defined. The papillae are few in number and are shallow. Cornification is absent (Fig. 6, A and B).



# CHANGES IN THE UTERINE AND PLACENTAL CIRCULATIONS DURING DIFFERENT STAGES OF PREGNANCY

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IN THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, of June, 1934, I described the anatomy and histology of the placental circulation. A review of this paper appeared in 1935. The present article is a continuation of that study and deals with pathologic changes in the placental circulation and anatomic changes in the uterine circulation during pregnancy.

## CIRCULATION OF NORMAL INVOLUTED UTERUS

Injection experiments of the normal involuted uterus show that it derives its blood supply from two main sources, the uterine and ovarian arteries. The hypogastric artery gives off two branches anteriorly before entering the transverse parametrium as the uterine artery; the inferior vesicalis and the lateral umbilical artery. No branches are given off while the uterine artery traverses the parametrium. As it enters the lateral wall of the cervix, in the region of the internal os, it gives off two branches, one descending and the other ascending.

The descending branch gives off numerous fine lateral branches to the musculature of the cervix and ends in the region of the portio by anastomosis with fine vessels in the upper lateral walls of the vagina. There is no definite circular artery around the cervix. The richest blood supply of the cervix and upper vaginal wall lies laterally. The midline of these organs receives only the distal peripheral stems coming from either side.

The ascending branch of the uterine artery divides into two main branches. These penetrate a little deeper into the musculature and subdivide in dichotomous fashion as they ascend toward the fundus where a latticework arrangement of vessels is seen. The midline of the uterus receives the peripheral branches from either side, therefore it is more anemic. The main lateral fundal branches travel medial to the external longitudinal layer of muscle and they give off at right angles numerous fine, corkscrewlike branches which penetrate the oblique and internal longitudinal layers of muscle and proceed toward the superficial layer of mucosa where they end by splitting into two or more fine, hairlike stems which often appear like small glomeruli (Fig. 1).

The corkscrewlike arteries destined for the mucosa allow for easy congestion of this part because the corrugations, or substituted valves, prevent backflow when the uterus contracts and favors superficial congestion of the mucosa in the premenstrual phase. They also provide for a rapid distention of the organ, as in early pregnancy, without narrowing

A very interesting fact observed in this study is the wide variations in degree of atrophy which occurred at comparable periods after cessation of menstruation. In the spontaneous menopause group, this varying tempo in the regressive process may be explained as due to the fact that although menstruation ceases, some estrogen production still continues in the ovaries for variable lengths of time. The degree of estrogen deficiency may, therefore, vary in patients after the menopause. In the case of x-ray castrates, there is probably also some residual estrogen activity in the ovaries which may vary in degree. The surgical castrates, strangely enough, also show variations in the degree of atrophy exhibited by the vaginal mucosa at similar intervals after bilateral ovariectomy. (No cases were included in this series in which there was any doubt as to the complete removal of both ovaries.) The possibility of a supernumerary ovary cannot, of course, be excluded. However, in view of the rareness of such an anomaly, this possibility need not be given serious consideration. The possibility that there may be some other source of estrogen formation in the body merits consideration.

#### SUMMARY AND CONCLUSIONS

1. Vaginal biopsies were taken from a group of 60 women with varying degrees of estrogen deficiency (menopause, surgical and x-ray castration). The degree of regression was compared with vaginal smears (prepared by the fuchsin method) before and after treatment with an active estrogen.

2. The vaginal smears and vaginal mucosa were classified into groups, representing various degrees of estrogen deficiency.

3. The vaginal smears according to this classification were found to correspond with graded degrees of atrophy of the vaginal mucosa.

4. After treatment with estradiol the changes in the vaginal smear reflected clearly the regenerative changes in the mucosa.

5. Atrophy of the vaginal mucosa was found in many cases not to be uniform in degree, being more marked in some areas than in others. The regenerative process resulting from estrogen administration likewise does not manifest itself uniformly.

6. Vaginal smears prepared by the fuchsin method were found to reflect the degree of regression as well as of regeneration of the vaginal mucosa in women.

7. The fuchsin vaginal smear method is recommended as a simple, reliable procedure for determining the presence of normal ovarian activity or estrogen deficiency, as well as an indicator of the efficacy of administered estrogens in cases of estrogen deficiency.

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details from a celloidin injection of an eight weeks' normal pregnant uterus which was injected by way of the aorta immediately after the death of the mother. Following the injection, the pelvic organs were removed and the uterus placed in running water for twenty-four hours to remove all traces of acetone. It was then opened down the midline anteriorly and the placenta was seen attached to the upper posterior fundal wall. The ovum was removed intact. Red celloidin, representing the maternal arterial circulation to the placenta, was found in the intervillous spaces of the placenta. This shows that there is an easy flow of blood into the intervillous spaces at this time of gestation. The musculature of the uterus was carefully corroded away by hydrochloric acid and a perfect cast of the uterine circulation remained (Fig. 2).

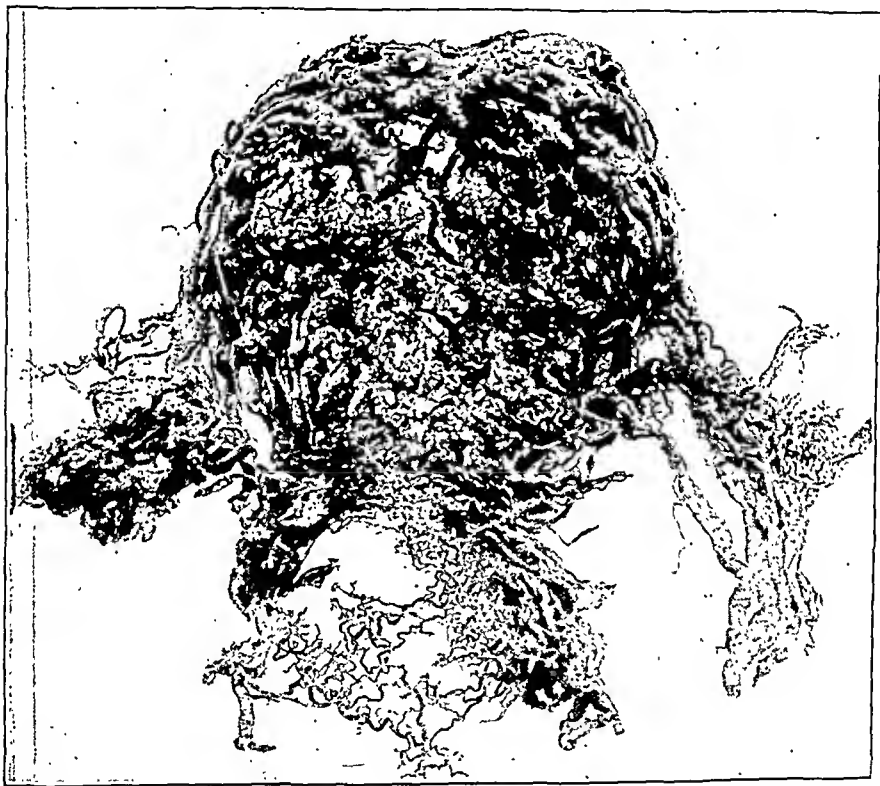


Fig. 2.—Celloidin injection of an eight weeks' pregnant uterus. Uterine arteries and veins injected. Note the uniform increase in new vessels to all parts of the uterus, including the cervix, and also to the vagina, broad ligament, and ovaries. The fine corrugations seen in Fig. 1 are retained in pregnancy.

The changes in the vascular arrangement of the uterus incident to an eight weeks' pregnancy are:

1. An increase in the number of newly constructed vessels. This is clearly shown in the fundus of the uterus, the lower uterine segment, cervix, the upper part of the vagina, and in the corpus luteum region of the ovary.

2. Instead of two main branches arising from the ascending branch of the uterine artery there are now nine vessels, some of which are elongated and enlarged tributaries of the two main vessels. As in the nonpregnant

their lumina. The anatomic arrangement of the uterine vascular tree is, therefore, constructed in such a manner as to accommodate for immediate functional demands whether it is during menstruation or early pregnancy. The veins in the involuted adult uterus follow the course of the arteries. The venous system, however, is less corrugated, the anastomosis is more free, and the tendency to pass beyond the midline of the fundus is greater.

The anastomosis between the uterine and ovarian arteries is very intimate and free. The main ascending uterine branch gives off two branches toward the tube on either side. The larger one pierces the outer muscle layer of the uterus about 2 cm. below the isthmus of the tube and extends laterally toward the hilus of the ovary. The other, finer branch extends from the cornu of the uterus into the tubal musculature. In the



Fig. 1.—A celloidin injection of a normal involuted multiparous uterus. The artery and vein on the left side were injected. Artery on right side alone injected. With a hand lens one can easily see the corrugation in the transverse portions and the splitting in the terminal arterioles.

region of the hilus of the ovary, there is a very rich anastomosis between the uterine and ovarian arteries. There appears to be an equal number of branches coming from the uterine as from the ovarian branch. Injection of the uterine artery alone proves this by showing a rich blood supply to the ovary, whereas injection of the ovarian artery alone shows a less reciprocal flow toward the uterus as did the uterine artery toward the ovary. From this conjointly formed, rich anastomosis in the hilus of the ovary, numerous parallel perpendicular branches enter the hilus in enormous numbers and appear as corrugated stems. This anatomic arrangement should favor congestion of the ovary, especially in the region of the developing corpus luteum, because numerous branches are attracted toward this area.

#### CIRCULATION OF THE PREGNANT UTERUS

Is the circulation of the pregnant uterus similarly constructed to that of the nonpregnant one? I was successful in getting the most minute

A close observation with a hand lens of the vessels and sinuses in the placental site region shows numerous interesting points. A relative increase in the thickness of the vascular area is seen. The blood sinuses are arranged in a definite anatomic way. The outer sinuses are flat and lie parallel to the surface. These represent the blood sinuses in the external longitudinal layer. The middle strata have numerous irregularly placed, oblique and transverse sinuses which form a spongelike layer. These sinuses lie between the internal and external longitudinal layers of the uterus. The inner layer of sinuses are like those of the external layer, coarse, flat, and lie parallel with the inner surface of the uterine cavity.

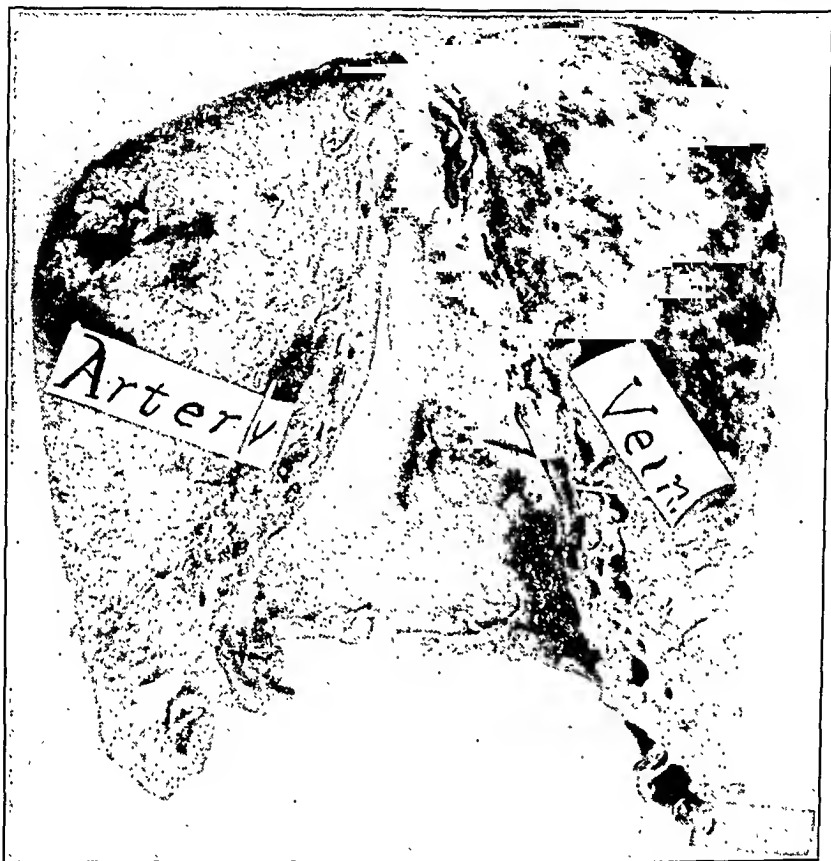


Fig. 4.—An inverted uterus. Shows the anatomical arrangement of the blood sinuses below the placental site.

In this anatomic arrangement lies the mechanism of control of hemorrhage after separation of the placenta in that the internal and external longitudinal layers of muscle and the oblique muscle fibers retract causing compression and torsion upon the sinuses in the middle layer of the uterine muscle; whereas the longitudinal parallel sinuses situated in the inner and outer longitudinal layers are only mechanically pressed upon by contraction and retraction of the longitudinal layers.

#### RELATION OF UTERINE SINUSES TO INTERVILLOUS SPACES

The anatomic arrangement of the blood sinuses in the uterine wall is shown in Fig. 4. This uterus was removed from a patient who had died

uterus, these branches are given off in dichotomous, palmlike fashion and extend like a canopy over the fundus, but not going beyond the midline of the organ. The arteries, for a considerable distance proximal to their endings, are corrugated, especially the transverse ones.

Examining the interior of the cast (Fig. 2) one notices innumerable transverse, corkserewlike vessels going to all regions of the decidua vera. In the region of the decidua basalis there is a greater number of similarly arranged vessels. Here they are running in parallel rows, are larger and longer than those in the decidua vera, and are in advance of the veins. One can easily understand, from examining such a cast, how easily a uterus bleeds when traumatized by abortion, and how extensive and rapid the spread of infection would be.



Fig. 3.—Celloidin injection of a seven months' pregnant uterus. Note the decrease in the number of vessels to the placenta-free side of the uterus and the relative increase in the number of sinuses below the placental site.

#### UTERINE CIRCULATION AT THE SEVENTH MONTH OF PREGNANCY

The uterine circulation at seven months' pregnancy, as shown by celloidin cast (Fig. 3) shows a marked anatomic change over that of the two months' gestation. The concentration of blood sinuses to the placental site region is pronounced. The placenta-free wall of the uterus shows atrophy of fine vessels and only a few coarse arteries with their corresponding veins are seen. The arteries still retain their corkserewlike arrangement but are larger, more direct in their course, and less in number than the two months' pregnancy. The arteries of the tube and corpus luteum of the ovary are also larger, coarser, and show disappearance of their finer branches.

these venous sinuses frequently occurs, but the thrombus cannot easily get away into the general circulation because of the anatomical arrangement of the in-going and out-going narrow vessels which traverse the internal and external layers of uterine muscle.

Where does the maternal endothelium end in the placenta? Fig. 5 shows a placenta which was specially treated to show this. The placenta, when expressed, was immersed in warm saline. With the aid of a high power hand lens small openings were seen in the decidua basalis portion of the placenta. These openings were packed with small pieces of gauze and the placenta immersed in 10 per cent formalin for a week. The pieces of gauze were then removed. The specimen shows the terminal portions of the spongiosa vessels ending in the decidua basalis. Microscopic study of sections taken through these areas show that maternal endothelium does not line any portion of the intervillous spaces.

These small maternal vessels, or channels, in the decidua basalis are more narrow than those in the spongiosa. This hour-glass effect of the vessels through the decidua favors congestion in the intervillous spaces. This arrangement also tends to prevent blood clots, when formed in the intervillous spaces, from escaping into the general circulation.

#### CIRCULATORY CHANGES IN PLACENTAL VESSELS

In the placenta is a vast, fine circulatory bed susceptible to toxic or bacterial stimuli. Rieker's theory of inflammation can be applied here. In the early stages of infection of the placenta there is a primary constriction of the villous vessels, later followed by dilatation proportionate to the degree of inflammation present. This is shown by section study and injection experiments.

In rapidly produced toxemias a congestion is seen in both maternal sinuses and in villous vessels. In milder forms of toxemias there appears to be a primary constriction of villous vessels; but in stronger, rapidly produced toxemias, there is a permanent dilatation and congestion in these vessels. This permanent dilatation of vessels leads to structural changes in the walls by producing an active proliferation of endothelium and connective tissue into the lumen of the villous vessels and hence finally reduces the blood flow. This constriction, or dilatation, in vessels may be local or generalized.

Eclampsia produces, in a normal placenta, marked congestion of the peripheral vascular tree, but a placenta showing marked senile or sclerotic changes before eclampsia occurs is comparatively free from involvement, because such placentas with their thick, hyperplastic vessels and marked reduction in the finer capillary bed do not react to toxic or physiologic stimuli. The true eclamptic placenta, therefore, differs from the one associated with chronic nephritis in that the latter goes on functioning in a permanently deficient manner, as is seen in the arterio-sclerotic kidney. Anoxemia in the fetus during eclampsia is partly due to adverse circulatory behavior. The fetus loses large quantities of blood into the villous vessels, and this, along with slowing of the stream in the intervillous spaces, predisposes to asphyxia of the fetus (Fig. 6).

from cardiac disease at term. At autopsy the cervix was manually dilated and the fetus extracted. The autopsy table was then put in the extreme Trendelenburg position and the uterus was filled with water. The cervix was sewed over tightly and the uterus was removed intact and suspended in 10 per cent formalin for a week. It was then incised through the anterior surface, passing through the placental site, and the placenta pushed inward. The uterus was then inverted in order to bring the sinuses closer to the surface when mounted.

With the aid of a high power hand lens one notices that the sinuses are not seen beyond the placental site region, and that the larger, elliptical and oblique sinuses lie for the most part between the internal and external longitudinal layers of muscle. These longitudinal contracting muscle layers are less pronounced as the cervix is approached. This explains why hemorrhage is more difficult to control when the placenta is situated low in the uterine cavity.

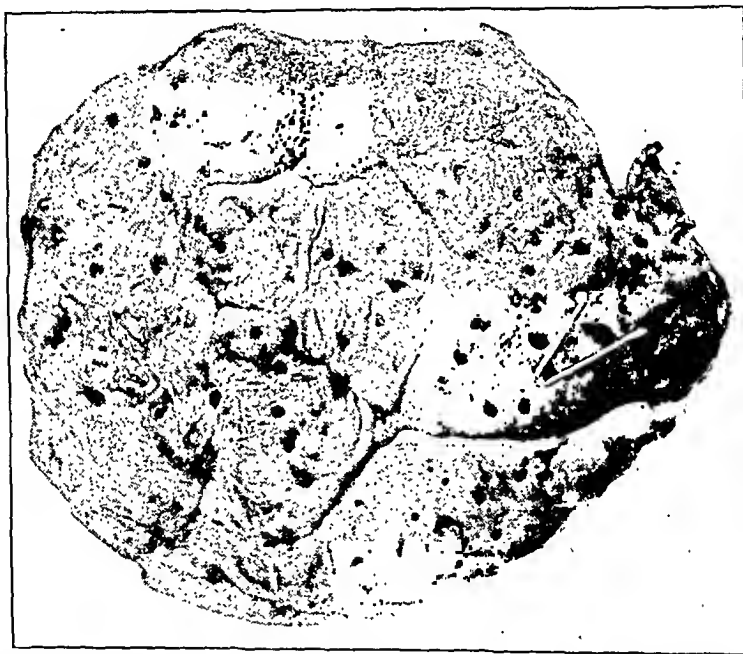


Fig. 5.—Maternal surface of normal full-term placenta showing the small fenestrae which represent the terminal portions of the spongiosa vessels which end in the decidua basalis.

It is interesting to note that into these arterial and venous sinuses are seen numerous small entrances having much the same architecture as the coronary vessels entering into the sinus of Valsalva of the aorta. These can be traced deeply into the musculature of the uterus and represent nutritional vessels to the uterus itself.

The blood in the venous sinuses is made venous from two sources: one from the intervillous spaces of the placenta, and the other from the returning deoxygenated blood from the uterine muscle itself. The most interesting point to me was the size and irregularity of shape of these sinuses, and that thrombosis did not occur more frequently. The uterine contractions must help to keep the blood flow onward. Thrombosis of



The vascular arrangement of the young placenta has already been described.<sup>3</sup> From the fifth month onward the placenta gradually becomes stripped of its fine peripheral branches. The fine anastomosis is missing and each half of the placenta is more dependent upon its respective cord artery. The villous vessels begin to retract, become less diffuse, and get more direct in their course. These points are clearly shown by injection of the vascular tree at different age periods.

The primary change, then, is in the villous vessels. They retract toward the center of the villus, and when this occurs Langhan's layer of epithelial cells begins to disappear. Combined Van Gieson and Weigert's stain shows an increase of connective tissue about the fine villous vessels. Elastic tissue fibrils are seen lying outside the endothelium. Finally the more distal and finer villous vessels become obliterated in one of two ways: either connective tissue grows into the lumen and obliterates it, or hyalinized connective and elastic tissue elements compress the capillary from without. The result of such changes is a gradual obliteration of the villous vessels and increased peripheral resistance is established. This causes back pressure and slowing in the stream. The result is dilatation in the arteriole at the base of the villus and finally in the subamniotic arteries. There now exists a continuous venous congestion of the placenta because gradual obliteration of the villous arterioles causes slowing in, and consequent dilatation of, the collecting venous sinuses of the villus. These changes are constant and orderly in occurrence.

According to Thoma<sup>4</sup> any agent which dilates a vessel wall or decreases velocity in current gives rise to increased pressure on the intima. The late result of back pressure and dilatation is hypertrophy in the arterial coats, later expressed mainly by an irregular intimal hyperplasia or sclerotic plaque along the intima. Finally the lumen is narrowed by proliferation of elastic and connective elements of the intima into the lumen, often totally obliterating it. Usually the embedded part of the subamniotic vessels shows a greater tendency to this irregular thickening of the intima.

The cause of this irregular hypertrophy in the subamniotic vessels can be easily explained by studying the anatomic changes occurring in these vessels. The large subamniotic trunks in the young placenta receive many fine, nourishing vessels which are given to them in the region of the chorionic membrane. I was able to demonstrate this point by careful injection experiments (Fig. 7).

About the fifth month of intrauterine life, the chorionic mesoderm plate begins to show a transition to fibrous tissue. This is often a rapid and extensive process. The fine vasa vasorum leading to these vessels now becomes shut off. This sets up irregular localized nutritional defects in the arterial wall which results in weakening, as is shown by irregular sacculations and puckerings in the vessels.

The response to dilatation is hypertrophy, which is in this case irregularly laid down. This produces interrupted localized areas of proliferating elastic and connective tissue; in other words, irregular sclerosis of the arteries. The picture of this sclerosis is similar to that seen in the

The result of such adverse circulatory behavior is interpreted in terms of stasis. Starling showed, in 1894, that in certain organs the capillaries are normally permeable to protein to such a degree that the effective osmotic pressure becomes lower than the capillary pressure, consequently the filtration of lymph through the capillary wall is constantly taking place. Stretching of the endothelium, as results from extreme degree of dilatation, allows for increased permeability, hence the colloids tend to drain off. The osmotic pressure of the human blood is about 6.5 atmospheres, the greater part being due to colloids and inorganic salts. The high colloid osmotic pressure of the blood in normal states prevents filtration edema. Stasis resulting from extreme dilatation of vessels favors increased permeability and a resulting rubrostasis, or adhesiveness of blood cells, is seen in the fine villous vessels in such states.



Fig. 6.—X-ray photograph of barium-gelatin injection of a full-term placenta removed during eclampsia. Note the marked peripheral congestion in the villous vessels. This is best shown by stereoscopic examination.

#### STRUCTURAL CHANGES IN PLACENTAL VESSELS

The structural changes occurring in the placental vessels have been described in terms of ageing by Fraser.<sup>2</sup> His experiments showed the sum total of definite orderly sequences in anatomic changes, in the construction of the organs, and their relations. A description of senile structural changes should be classified as a physiologic phenomenon and only becomes pathologic when an exaggeration in this normal physiologic sequence occurs.

The author studied structural changes in placental vessels by means of barium and celloidin injection followed in each case with numerous histologic sections stained by hematoxylin and eosin, Van Gieson, and Weigert's connective and elastic tissue stains. In order to restrict the number of photographs, only the celloidin injections will be shown in this article.



Fig. 8.—Celloidin injection of a full-term, markedly senile placenta. Note the decrease in the number of villous vessels with atrophy at the periphery. The villous vessels are more direct and coarser in arrangement.

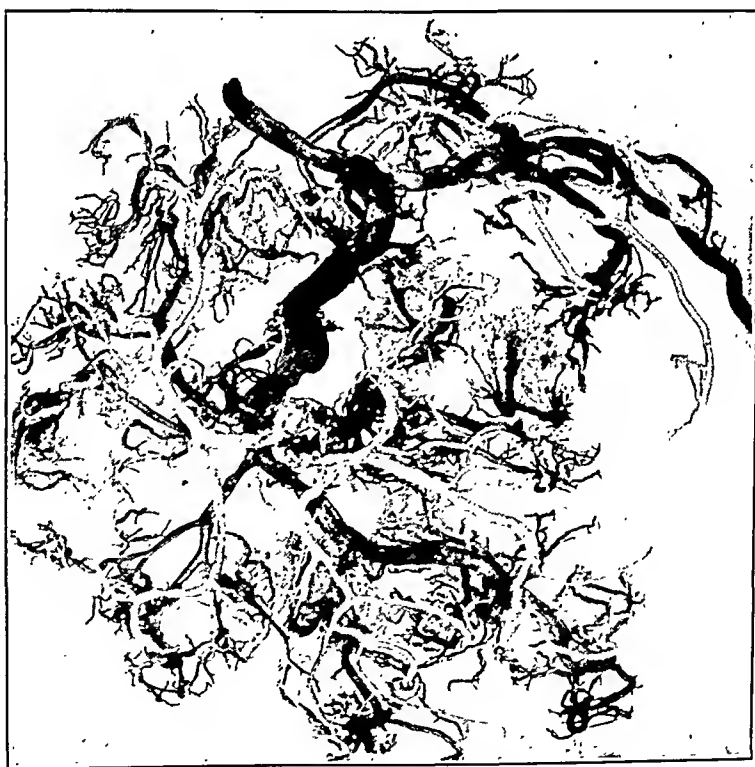


Fig. 9.—Celloidin injection of full-term, thick, grayish placenta. Injection showed only 7 functioning tufts of vessels, yet the fetus was born alive.

cord vessels. At first, there is an increase in the internal elastic tissue lamina, which is seen as wavy black bands. This is followed by hypertrophy in the external elastic tissue lamina, and finally by a rapid proliferation of connective tissue and elastic tissue elements into the lumen of the vessel, greatly reducing its caliber. Narrowing of the vessel lumen results in progressive anemia in the placenta.

Occasionally these large subamniotic vessels become totally obliterated and new collaterals or recanalization of the occluded vessel is seen. If degeneration ensues, then we see by the combined stain, masses of hyalinized elastic tissue products lying in the vessel wall. Staining with sudan III demonstrates fatty degeneration by showing fine particles of degenerated fat in the media and intima.

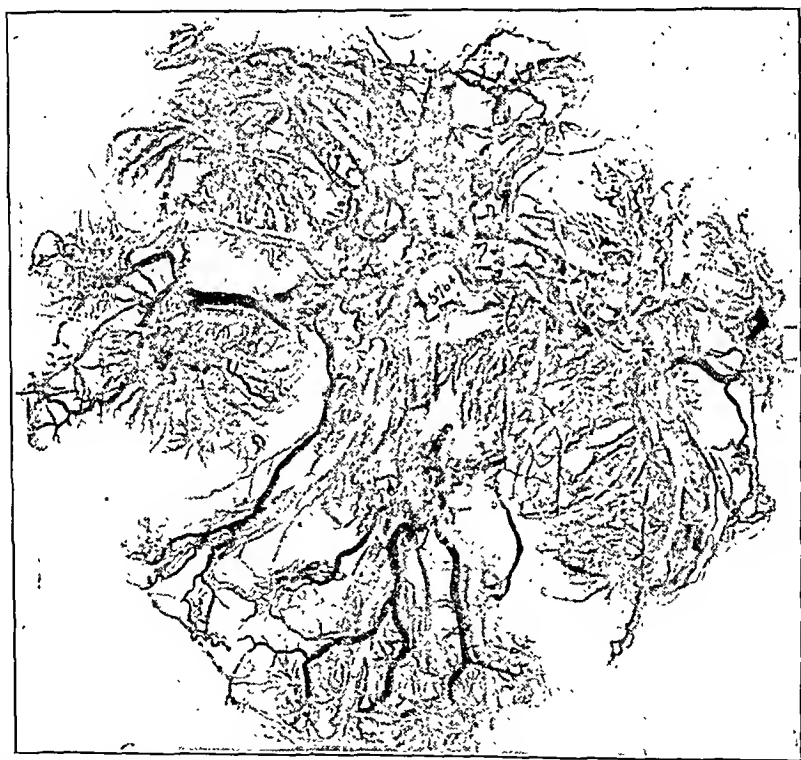


Fig. 7.—A celloidin injection of a normal six months' placenta. Note the thinness of the circulatory bed at this period of gestation. Under high magnification small hairlike stems are seen attached to the large subamniotic vessels.

The veins show similar changes, but not so early in the life history of the organ. The tissue response is less marked because the vein wall is less endowed with elastic and muscle tissue. A common finding, therefore, is a marked irregular permanent dilatation in the subamniotic veins.

A common accompaniment of arteriosclerosis is hyalinization. This degenerative process, however, is never very prominent in the placental vessels. Degenerating clumps of elastic and fibrous tissue products are seen lying in the intima, and from here it spreads to involve the media.

# THE COMPLICATIONS ASSOCIATED WITH EXCESSIVE DEVELOPMENT OF THE HUMAN FETUS\*

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## INTRODUCTION

THE average weight of infants born in the United States has been found by different investigators to be about 3,390 gm. Provided the pelvis is not contracted, it is rare for infants weighing less than 4,500 gm. to give rise to dystocia due to size. It has been found, however, that delivery of an infant weighing more than 4,500 gm. is frequently attended with serious difficulties resulting in a surprisingly high fetal and maternal mortality. Since facilities for study of a large series of excessively developed fetuses were available, this analysis was undertaken to point out the possible causative factors, the complications of labor, and the injuries to the mother and child in an attempt to make possible more accurate diagnosis and adequate treatment.

A search through the literature reveals that although excessive development of the fetus has been a matter of interest for many hundreds of years, most papers do little more than report the birth of giant infants.

The record for the largest baby is claimed by a patient of Dr. Belcher<sup>1</sup> of Sale City, Georgia. She gave birth to a 25 pound stillborn infant. This claim has not been allowed because the physician failed to describe the type or condition of the scale on which the infant was weighed. Ortega<sup>2</sup> in 1891 reported the birth of a 24 pound 13 ounce Italian boy. This case also lacks proof. The largest baby whose weight was carefully verified was born at the Louise Margaret Hospital in Aldershot, England. As reported by E. L. Moss,<sup>3</sup> it was the patient's second pregnancy and five days before the calculated date she gave birth to a 24 pound 2 ounce stillborn infant. As far as can be determined from the literature there is no record of any infant born alive weighing more than 15 pounds. In this study of 195 cases, the greatest weight was 13 pounds 2 ounces.

The occurrence of infants weighing 4,500 gm. or more at birth is not uncommon. At the Chicago Lying-in Hospital during the years 1931 to 1939 there were 20,219 births. In this series, 195 children weighed, 4,500 gm. or more, an incidence of 0.94 per cent. Of these, 177 weighed between 4,500 and 5,000 gm.; 13 between 5,000 and 6,000 gm.; and 1 over 6,000 gm. In Europe the highest incidence, 2.2 per cent, was found by Pape<sup>4</sup> in Osnabruck. In Kiel, Fuchs<sup>5</sup> detected 1.35 per cent. Both Pflüger<sup>6</sup> and Zangemeister<sup>7</sup> report 0.58 per cent. Kishimoto<sup>8</sup> in Japan reports 0.4 per cent. Among a total of 24,644 births, Kaern<sup>9</sup> of Copenhagen found 228 infants weighing 4,500 gm. or more, an incidence of 0.92 per cent. In 23,500 consecutive deliveries at the Johns Hopkins Hospital according to Guttmacher,<sup>10</sup> the figure was 1.07 per cent.

\*Read at a meeting of the Chicago Gynecological Society, March 17, 1939.

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In the villous vessels it appears as an edematous swelling of elastic tissue fibers outside the endothelium which presses upon and tends to obliterate the lumen of these fine vessels. Calcification occasionally follows upon hyalinization in the larger subamniotic vessels.

Hyalinization of the maternal surface of the placenta must not be mistaken for degenerative vascular changes. In this case combined Weigert, Van Gieson, hematoxylin and eosin stains show large masses of vitreous hyalinized epithelial cells and decidual tissue in and about Nitabuch's layer. The presence of such large masses of hyaline interferes with a free vascular flow toward the intervillous sinuses. Calcification frequently follows upon such hyalinized areas. Calcification of the maternal surface of the placenta, then, cannot be classified as a consequence of sclerosis occurring in the vessels.

#### RECONSTRUCTION IN PLACENTAL VESSELS

Preliminary injection with barium gelatin and celloidin of these placentas described histologically as senile or sclerotic shows that every vascular tree has the power to reconstruct itself if given time and if functional demands require it. This reconstruction is brought about by an orderly arrangement in its anatomic relationship. The extensive obliteration of fine villous vessels as a consequence of senile change is compensated for by the construction of new vessels which are less fine in their anastomosis, are more direct in course, and have a more simple vascular construction (Fig. 8). This allows for a quicker, more direct flow and thus compensates for a finer, more diffuse, slower flowing capillary bed, as is seen in the young placenta. This point is very clearly shown in one of my celloidin injections of the placenta where there are only 7 corallike, newly constructed tufts which did not involve over one-seventh of the placental surface, yet the fetus was born alive (Fig. 9). This placenta was easily and quickly flushed with saline, as was to be expected.

Reconstruction in the larger subamniotic vessels is less pronounced because the process of obliteration is slower. Several new collaterals are formed, or new vessels may grow within the old obliterating ones. This process is an orderly yet consistent one.

I am indebted to Mr. Wallace J. Plumpton for assistance in compiling this paper.

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TABLE II. DURATION OF PREGNANCY IN DAYS  
(Calculated from the First Day of the Last Menstrual Period)

	LESS THAN 272	273-294	MORE THAN 294	AVERAGE DURATION OF PREGNANCY
F. and H. Hotelling				
537 normal series	25.0%	65.5%	9.5%	281
L. Kraul				
8809 (3,000+ gm. fetus)	15.6%	70.7%	13.7%	280
Chicago Lying-in Hospital				
151 (4,500+ gm. fetus)	7.9%	54.9%	37.2%	288

It has been stated (Stander,<sup>19</sup> Eden<sup>20</sup>) that the large size of one or both parents contributes toward excessively large fetuses. According to Gregerson,<sup>21</sup> in Scandinavian countries where large size is considered a racial characteristic, the average birth weight of infants is 3,530 gm., while in this country, the average is stated to be 3,390 gm., a difference of 140 gm. In 137 cases of this series where the mother's weight prior to pregnancy was known, the average was 156 pounds, a figure which is considerably higher than the average weight in clinic practice. However, no predominant racial group was found.

It is generally agreed that multiparas have larger babies than primiparas. The increase is gradual, each child being slightly heavier than the previous one.

Zangemeister<sup>7</sup> in 1917 and Gregerson<sup>21</sup> in 1937 each studied a large series of cases from this standpoint and found that the birth weight of infants born to multiparas averaged 158 gm. more than those delivered by primiparas. In the present study there were 45 primiparas and 150 multiparas. The mean weight of the infants in the first group was 4,636 gm. and in the second group, 4,730 gm. Twenty-two per cent of the multiparas had given birth to five or more children. Moreover, 38 per cent stated that infants delivered in previous pregnancies weighed 9 or more pounds.

Male infants are frequently larger and heavier at birth than female infants. The average difference in a large series of normal cases is about 48 gm. In the present study of infants weighing more than 4,500 gm., there is a marked preponderance of male (67 per cent) to female (33 per cent) infants. Unexpectedly the females averaged 58 gm. more in weight.

Advancing age is often considered a factor in the production of excessively developed fetuses. In this study the average age for multiparas was 32 years and for primiparas 27 years.

Diabetes was a very insignificant causative factor in this series, as it occurred in only two women.

#### PREGNANCY

No complications of pregnancy were especially associated with over-development of the fetus except toxemia. This occurred in 27.3 per cent of the women in this study. Dieckmann<sup>22</sup> believes that large or obese women tend to have a higher blood pressure during pregnancy than women of normal size. Since these patients are above average weight it may be a contributing factor in the elevation of blood pressure.

The conditions most commonly causing excessive development of the fetus are prolonged pregnancy or unusually rapid growth of the fetus during a normal period of gestation, but large parents, multiparity, advancing age, and diabetes appear to be contributory factors.

The relationship between prolonged pregnancy and large fetuses was first demonstrated by Von Winkel<sup>11</sup> in 1905. This study has since been confirmed by Starcke,<sup>12</sup> Jacoby,<sup>13</sup> Zangemeister,<sup>7</sup> and others. Schultze,<sup>14</sup> however, argued that what appears to be a prolonged pregnancy may be due to fertilization during the latter half of the menstrual cycle. Assuming that impregnation may occur at any time during a twenty-eight-day cycle, there could be a variation of twenty-eight days in calculation of the date of delivery. Since Knaus,<sup>15</sup> Ogino,<sup>16</sup> and others have shown that in the great majority of women, fertilization occurs between the tenth and seventeenth days following the first day of menstruation, little variation in the length of gestation is to be expected on this basis.

The length of gestation calculated from the first day of the last menstrual period was studied in 537 women by H. and F. Hotelling<sup>17</sup> in 1932. These were women of superior intelligence, and it was felt that reliance could be placed on the stated date of the last menstrual period. This material showed the mean duration of pregnancy to be 281 days. Of these women, 77.8 per cent delivered between the 266th and 294th days; 12.7 per cent before and 9.5 per cent after this period. Kraul<sup>18</sup> (1935) selected and analyzed the histories of 8,809 women in whom the menstrual cycle was twenty-eight days. He observed that, although the mean duration of pregnancy was 280 days, 13.7 per cent delivered after 294 days. After this time pregnancy may be said to be prolonged since the great majority of births occurred within two weeks of the mean (280 days). These studies demonstrate that the duration of pregnancy shows a consistent individual variation, although according to Hotelling<sup>17</sup> all pregnancies in the same woman are likely to be of similar length.

An analysis of 1,000 consecutive deliveries at the Chicago Lying-in Hospital from the viewpoint of relation of weight of the newborn to duration of pregnancy clearly indicates the direct relationship between average weight and average duration of pregnancy. In other words, the larger the infant, the longer the duration of pregnancy (Table I).

TABLE I. RELATION OF WEIGHT OF NEWBORN TO DURATION OF PREGNANCY  
(1,000 CONSECUTIVE CASES—LYING-IN HOSPITAL)

INCIDENCE PER CENT	FETAL WEIGHT	MEAN DURATION OF PREGNANCY
0.3	1,500-2,000	243.7
3.9	2,000-2,500	259.4
14.1	2,500-3,000	275.2
41.5	3,000-3,500	282.8
29.3	3,500-4,000	285.2
9.3	4,000-4,500	287.2
1.2	4,500-5,000	292.1
0.4	5,000+	298.0

Of the 195 cases in this study, 151 were found to have normal regular menstrual periods and remembered the date of the last period prior to the onset of pregnancy. Of these, 7.94 per cent delivered before 272 days; 54.9 per cent between 272 and 294 days; and 37.08 per cent after 294 days. The mean duration of pregnancy was 288 days. These figures when compared with those of Hotelling<sup>17</sup> and Kraul<sup>18</sup> for normal pregnancy demonstrate the direct relationship between prolongation of pregnancy and excessive development of the fetus (Table II).



TABLE IV. COMPLICATIONS OF THE SECOND STAGE OF LABOR IN RELATION TO TYPE OF DELIVERY IN MULTIPARAS

TYPE OF DELIVERY	TOTAL CASES		DÜHRSSSEN'S INCISIONS	PERSISTENT OCCIPUT POSTERIOR	SHOULDER DYSTOCIA
Spontaneous	95	63.3%	0	0	20
Low forceps	12	8.0%	0	1	3
Midforceps	5	3.3%	1	3	3
High forceps	6	4.0%	2	2	3
Breech extraction	4	2.7%	0	0	2
Version and extraction	2	1.4%	0	0	0
Craniotomy	5	3.3%	0	0	0
Low cervical cesarean	18	12.0%	0	0	0
Porro cesarean	3	2.0%	0	0	0
Total	150	100.0%	3	6	31
			2.0%	4.0%	20.6%

Chicago Lying-in Hospital is 4.6 per cent. Dührssen's incisions were necessary in five instances; the average duration of labor prior to this operation was 55 hours. Maternal exhaustion, intra-partum infection, and failure of labor to progress after 12 or more hours with the cervix in all cases dilated 6 cm. or more were the main indications.

In multiparas forceps delivery was necessary in 23 or 15 per cent of the cases. There were 5 midforceps, 6 high forceps, and 12 low forceps operations. Dührssen's incisions were done in three instances. The indications for interference here were essentially the same as for primiparas. Where high forceps was done the average duration of the second stage of labor was two hours and ten minutes. In two cases the head persisted in the occipitoposterior position. The average size of the infant was 4,930 gm. and great difficulty was encountered with the shoulders. Despite these complications all of the infants delivered by high forceps survived.

*Breech Extraction:* Breech presentation was present in 4 multiparas and 1 primipara, a total of 2.5 per cent of the cases (the average for the hospital is 4.0 per cent). The 1 primipara was delivered by cesarean section. Excessive development of the fetus was the indication. Labor was not unusually prolonged in the multiparas, but in each great difficulty was encountered during delivery of the shoulders and head. In two of the 4 cases the fetuses died during delivery.

*Version and Extraction:* Version and extraction was done in three cases, 2 in multiparas and 1 in a primipara. In the primipara the head failed to engage after a prolonged labor. Following the version it was impossible to deliver the head without craniotomy. In the multiparas, version and extraction was done in one case because of a transverse presentation and in the other after attempts to deliver the infant with forceps had failed. Both infants lived.

*Craniotomy:* It was found necessary to perform craniotomy in 7 cases; 2 in primiparas and 5 in multiparas, a percentage incidence of 3.6, the average for the hospital clinic being 0.6 per cent. Three of the infants had succumbed before the onset of labor and the other four died during labor before the destructive operation was performed.

*Cesarean Section:* The incidence of cesarean section was 13.4 per cent, approximately two and one-half times the average (5.8 per cent) at the Chicago Lying-in Hospital. Twenty-one were done in multiparas and 5 in primiparas, an incidence of 14 per cent and 11 per cent, respectively. Table V shows the several indications for this operation.

In primiparas there were two elective cesarean sections. The indication for one was a funnel pelvis with the fetus in a breech presentation, and for the other a generally contracted pelvis with disproportion between the head and inlet. One woman with a contracted pelvis was given an eight hour test of labor during which period the head failed to engage. There were two women with normal pelvis who went into labor spontaneously, head not engaged but with no demonstrable disproportion. Following labors of twenty and twenty-seven hours, respectively, engagement failed to take place and low cervical cesarean sections were done. Apparently

## LABOR

The course of labor in patients with excessive development of the fetus is similar to that in women with generally contracted pelves. According to Zangemeister and Lehn,<sup>23</sup> it is rare for normal fetuses less than 4,500 gm. in weight to give rise to dystocia. On the other hand, when the fetus is excessively developed, the frequency of complications increases in proportion to the weight. This is especially true of primiparas.

*Length of Labor.*—In this study the average duration of labor was 29 hours 43 minutes for primiparas and 14 hours 20 minutes for multiparas, when delivery was effected by methods other than cesarean section. Labor was prolonged to almost twice the average length for the former and about 3 hours for the latter. The mean duration of the second stage of labor for primiparas was 2 hours 47 minutes and for multiparas 1 hour.

There were a number of factors in addition to the large size of the fetus which contributed to the marked prolongation of labor in primiparas. In 19 cases the head was not engaged during the early period of labor. There were ten instances in which the occiput was in the posterior position, all persisting as such and requiring manual or forceps rotation to the anterior position before delivery could be accomplished. Secondary uterine inertia was a frequent complication.

In multiparas, labor was unduly prolonged only in association with abnormal presentations, such as transverse or breech, or when the weight of the fetus approached 5,000 or more grams. Of 22 cases with the occiput in the posterior position, 16 delivered spontaneously; 3 required manual rotation and midforceps; 2 high forceps; and 1 low forceps. Breech presentation occurred four times in multiparas and only two children survived the labor.

From this series of cases it must be concluded that the association of posterior position with excessive development of the fetus is unusually frequent, especially in primiparas, and produces serious dystocia.

TABLE III. COMPLICATIONS OF THE SECOND STAGE OF LABOR IN RELATION TO TYPE OF DELIVERY IN PRIMIPARAS

TYPE OF DELIVERY	TOTAL CASES	DÜHRSEN'S INCISIONS	PERSISTENT OCCIPUT POSTERIOR	SHOULDER DYSTOCIA
Spontaneous	13 28.9%	0	0	7
Low forceps	11 24.4%	1	4	4
Midforceps	13 28.9%	3	6	4
High forceps	0	0	0	0
Breech extraction	0	0	0	0
Version and extraction	1 2.2%	0	0	0
Craniotomy	2 4.4%	1	0	0
Low cervical section	5 11.2%	0	0	0
Porro cesarean	0	0	0	0
Total	45 100.0%	5 11.1%	10 22.2%	15 33.3%

*Method of Delivery* (Tables III and IV).—Mechanical intervention, including cesarean section, was necessary in 44 per cent of the cases in this series, while the average for the Chicago Lying-in Hospital is 30.4 per cent. The incidence of intervention was almost twice as great in primiparas (71 per cent) as in multiparas (37 per cent).

*Forceps:* The usual indications for low and midforceps both in primiparas and multiparas were lack of progress and prolongation of the second stage of labor. The large fetal head, the frequency of persistent occiput posterior positions, and maternal exhaustion were responsible for this. Abnormality of fetal heart tones was occasionally the indication for intervention.

In primiparas forceps were used in 24 (53 per cent) of the cases, 28 per cent being difficult midforceps. In primiparas the average incidence for midforceps at the

*Third Stage of Labor:* The third stage of labor was frequently complicated by retention of the placenta and atony of the uterine muscle. Of 169 patients delivered through the birth canal, 35 (18 per cent) developed post-partum hemorrhage, 16 per cent occurred in spontaneous and 28 per cent in operative deliveries. The average incidence of post-partum hemorrhage at the Chicago Lying-in Hospital is 3.4 per cent. In 11 cases the blood loss was over 1,000 c.c. Manual removal of the placenta was necessary in 10 patients and in six the uterus was packed in order to control hemorrhage.

It is probable that in addition to the unusual stretching of the uterine muscle caused by the large fetus, prolonged labor, maternal exhaustion, and long anesthesia were additional factors responsible for the higher incidence of hemorrhage in complicated deliveries.

#### MORBIDITY AND MORTALITY

*Maternal Morbidity:* The morbidity was 30 per cent for the entire group of 195 cases studied. The increased frequency of prolonged labor, surgical intervention, and post-partum hemorrhage were probably contributing factors producing the high incidence of infection. The morbidity for spontaneous deliveries was 14 per cent while the morbidity for operative deliveries other than cesarean section was 40 per cent and for cesarean section, 77 per cent. Of the 58 morbid cases, 9 patients had severe puerperal sepsis and 2 developed femoral thrombophlebitis.

*Maternal Mortality:* There were 2 maternal deaths, 1 from shock and 1 from puerperal infection. The first was a 38-year-old para vii who was admitted to the Chicago Lying-in Hospital with a history of prolonged labor and intra-partum infection. Examination showed the cervix fully dilated, head not engaged, and the fetal heart was not heard. A diagnosis of intra-partum death of the fetus was made and a craniotomy was performed. The patient went into shock and died forty minutes following delivery. Autopsy permission could not be obtained. The fetus without cranial contents weighed 5,140 gm.

The second death occurred in a 24-year-old primipara who had a thirty-four-hour labor, difficult midforceps delivery, and post-partum hemorrhage. Examination of the birth canal immediately following delivery revealed a tear in the vagina extending into the right broad ligament. Hemorrhage was controlled by pack. The patient subsequently developed a severe puerperal infection and died fifty-five days following delivery. An autopsy was obtained which showed generalized peritonitis and septicemia.

TABLE VI. TIME OF INFANT AND FETAL DEATH IN RELATION TO TYPE OF DELIVERY

	ANTE PARTUM	INTRA PARTUM	NEONATAL
Spontaneous	2	1	1
Low forceps			
Midforceps		3	2
High forceps			
Breech extraction		2	
Version and extraction		1	
Craniotomy	3	4	
Low cervical cesarean			
Porro cesarean		1	
Total	5	12	3

*Fetal Mortality* (Table VI): The fetal mortality including both stillbirths and neonatal deaths was 10.3 per cent. For primiparas it was 13.3 per cent and for multiparas it was 9.6 per cent. The total infant and fetal death rate for the hospital among those who weighed 2,500 gm. or over is 1.9 per cent. A comparison of the two figures shows that the mortality for excessively developed fetuses is five times as great as that for all those weighing over 2,500 gm. Although this figure appears high it is lower than those given by some other writers for similar groups of cases. T. Kaern<sup>9</sup> who recently studied a group of 228 excessively developed infants, weighing 4,500 gm. or more, reports a fetal mortality of 14.9 per cent. Starek<sup>12</sup> reports 10.5 per cent. Zangemeister<sup>7</sup> points out that beginning with 4,500 gm. the mortality

TABLE V. INDICATIONS FOR CESAREAN SECTION

	PRIMIPARAS	MULTIPARAS
<i>Low Cervical Section:</i>		
Contracted pelvis, elective	2	1
Contracted pelvis, elective, repeat		3
Contracted pelvis, test of labor	1	4
Normal pelvis, test of labor	2	4
Normal pelvis, elective, repeat		3
Sterilization		3
<i>Porro Cesarean:</i>		
Ruptured uterus (old cesarean scar)		1
Intra-partum infection (face presentation)		1
Threatened rupture (aged 45, para xii)		1
Total	5	21

in the latter cases the excessive size of the fetus was not recognized as the cause of the failure of the head to engage or the patient would probably have been subjected to a much shorter test of labor.

In multiparas, 4 elective cesarean sections were done because of contracted pelvis. Three of these had had previous cesarean operations. In 4 women with contracted pelvis where cesarean section was done after a test of labor, the patients had previously given birth to large stillborn infants. The average duration of labor prior to operation in these cases was fifteen hours. In the group of 4 multiparas with normal pelvis who were in labor prior to cesarean section, all had delivered one or more normal-sized infants through the birth canal without unusual difficulty. The average duration of labor in this group before cesarean section was performed was nineteen hours. The membranes had been ruptured for six or more hours and the head had failed to engage. In the latter group the average size of the infant was 4,790 gm. These examples make it apparent that a normal pelvis may occasionally be inadequate for the noninjurious delivery of an excessively developed fetus. There were no fetal or maternal deaths in the patients delivered by low cervical cesarean section.

It was found necessary to remove the uterus during cesarean operations in 3 multiparas. The indications for one was a ruptured uterus, the rupture taking place through the scar of a previous classical cesarean section. The mother lived but the infant was stillborn. The indication for the second operation was threatened rupture of the uterus in a 45-year-old multipara, having her twelfth full-term pregnancy. In the third case there was evidence of intra-partum infection, a face presentation, and failure of the cervix to dilate after twenty-six hours of irregular pains.

*Perineal Injury:* The complications associated with delivery were frequent. Despite the fact that episiotomy was done in 114 of the 168 patients delivered through the birth canal, there were three third degree tears, many instances of deep extension of the perineal incision, and extensive vaginal ruptures. Lacerations of the cervix were severe enough to produce bleeding and require repair in twelve cases.

*Shoulder Dystocia:* Frequently serious difficulty was encountered with delivery of the shoulders. Of 168 deliveries through the vaginal canal, 46 or 27 per cent of the cases were associated with shoulder dystocia. The average shoulder circumference in this group was 39 cm., 5 cm. larger than that of normal-sized infants. In at least 2 cases this complication was responsible for death of the fetus. In 7 cases undue traction on the head or pressure in the axilla produced serious injuries to the brachial plexus. Delivery of the shoulders was accomplished by a combination of methods: pressure on the anterior shoulder above the symphysis, twisting the shoulders into the transverse or oblique diameters of the pelvic inlet, or bringing down the posterior arm and shoulder into the hollow of the sacrum. In one case it was necessary to use a blunt hook in the posterior axilla in order to effect delivery of the shoulders.

The presenee of any of these factors should be an indication for intra-uterine mensuration of the fetal head if facilities are available. Several investigators (Clifford,<sup>26</sup> Thoms,<sup>27</sup> Hodges,<sup>28</sup> Ball,<sup>29</sup> etc.) have devised methods for the measurement of the fetal skull before delivery and predietion can be made with varying degrees of accuraey as to its size. The diameter and circumference of the head are directly related to the size and weight of the fetus. Where facilities for stereoroentgenometry are available the x-ray is of inestimable value in the ante-partum diagnosis of exsessive fetal size.

The obstetric management of patients who give evidence of exsessive development of the fetus depends on the degree of disproportion. In patients with contracted pelves, an elective cesarean section is the method of choice. In this series of cases there were 17 patients with contracted pelves. Of the 5 delivered through the birth canal, 3 infants were still-born. On the other hand, 12 cesarean sections were done for this indication with 1 fetal and no maternal mortality. Though the number of cases is small, the results are significant (Table VII).

TABLE VII. TYPE OF CONTRACTED PELVIS IN RELATION TO MORTALITY AND METHOD OF DELIVERY

	SIMPLE FLAT PELVIS	GENERALLY CONTRACTED PELVIS	FUNNEL PELVIS	INFANT AND FETAL MORTALITY
Spontaneous	0	0	0	0
Low forceps			1	0
Midforceps			1	1
High forceps		1		0
Craniotomy	1		1	2
Low cervical cesarean	6	4	1	0
Porro cesarean	1			1
Total	8	5	4	4

When there is doubt about the degree of disproportion, a test of labor should be given. If the head does not engage within a safe period of time, cesarean section seems to be the best method of delivery. In primiparas where the labor has a greater tendency to be prolonged and where the frequency of serious mechanical intervention and fetal mortality are higher, a shorter test of labor should be given in the interest of both the mother and the child.

In multiparas when the head is engaged or can be impressed into the pelvis, it is clear that the chance for uncomplicated delivery is good. The same holds for primiparas except for those where the head of the fetus is in the posterior position. As was pointed out earlier in this study, labors in these cases are likely to be prolonged, and the second stage is frequently complicated by failure of the head to rotate.

Stander,<sup>19</sup> Kaern,<sup>9</sup> Zangemeister,<sup>7</sup> and others have recommended induction of labor in cases of abnormally large fetuses. There are two main reasons for this indication. It has been shown by Zangemeister,<sup>7</sup> Kaern,<sup>9</sup> and others that chance of the child's being born alive decreases with each additional 500 gm. of weight. The danger to the fetus is mainly due to the dystocia caused by the increased weight. Moreover when pregnancy is prolonged the fetus has a greater tendency to die prior to the onset of labor than is otherwise true.

is directly proportional to the increase in size and weight. He states the mortality for fetuses weighing between 5,000 and 6,000 gm. is 29 per cent, for those from 6,000 to 7,000 gm. is 85 per cent, and for 7,000 gm. or over, 100 per cent.

Of 6 fetal deaths associated with maceration, 5 occurred prior to the onset of labor. Zangemeister and Lehn,<sup>23</sup> Kaern<sup>9</sup> and others report a 3 to 4 per cent incidence of ante-partum deaths in excessively developed fetuses. These authors have observed that this condition is frequently associated with excessive prolongation of pregnancy but no satisfactory explanation for cause of death can be found. In this connection the work of Snyder,<sup>24</sup> Koff and Davis,<sup>25</sup> and others, in the artificial prolongation of pregnancy in the rabbit is of interest.

They found that pregnancy could be prolonged from the normal length of thirty-two days to any desired time up to sixty days. This was accomplished by the production of fresh corpora lutea from the intravenous injection of gonadotropic hormones (Snyder<sup>24</sup>) or by the administration of daily doses of progesterone (Koff and Davis<sup>25</sup>). From the thirty-second to the thirty-sixth day each day's retention of the fetus within the uterus caused an increase in growth so that by the thirty-sixth day the average weight had increased from 55 gm. (average weight when labor occurs normally on the thirty-second day) to 80 gm., a net increase of 45 per cent in four days. When pregnancy was prolonged beyond the thirty-sixth day, intrauterine death of the fetuses invariably occurred and none was ever born alive. In other words, at thirty-six days the period of postmaturity compatible with survival of the fetus ends. No pathologic changes could be found to account for this phenomenon.

Other writers have ascribed ante-partum death of the postmature fetus to placental degeneration, but it is generally agreed that no consistent pathologic change is noted except calcification. It is noteworthy that in all five instances of ante-partum death of the fetus in our series the duration of pregnancy was 297 days or more.

In the nonmacerated fetuses there were four cases of intracranial hemorrhage. Of these, 3 were associated with difficult midforceps deliveries and 1 occurred during spontaneous delivery. Asphyxia was the most frequent cause of death and occurred in 11 fetuses. In 2, this was due to prolapse of the cord before the cervix was fully dilated; in 2 cases it was associated with breech extraction; and in 1 it was caused by rupture of the uterus. The others occurred during difficult forceps and shoulder deliveries.

#### DISCUSSION

The high incidence of difficult obstetric operations and the number of prolonged labors ultimately ended by cesarean section serve to indicate that the large size of the fetus is frequently missed or that recognition occurs too late for safety. Consequently the mother may be subjected to the risk of a major operation in the interest of the child, or the child may be sacrificed in the interest of the mother. If excessive development of the fetus could be recognized before the onset of labor, the unusually high maternal and fetal mortality could, without doubt, be reduced. Unfortunately there is no reliable sign or collection of signs by which antenatal diagnosis of abnormal size of the fetus can be definitely established except perhaps in extreme cases.

An abdomen of unusual size, when multiple pregnancy and hydramnios have been eliminated as possible causes, is the most valuable sign of an oversized fetus to the experienced obstetrician. This observation, associated with a large unengaged head and inability to impress the head into the inlet of a normal pelvis, should arouse suspicions that the fetus is abnormally large. In multiparas a history of the delivery of one or more large children is of importance. If one or both parents are large, if pregnancy is prolonged, and if diabetes mellitus is present in the mother, the probability of excessive development of the fetus is increased.

ment of the onset of labor beyond the usual time. The question then arises as to what brings about such alteration in the time of onset of parturition.

There is much experimental evidence that the time of emptying of the uterus is under hormonal control. For instance, in the rabbit, one may start with normal animals and superimpose a new timing mechanism upon that of normal pregnancy. Koff and Davis have done this by the injection of progesterone in rabbits near term, thus augmenting the animals' store of this material which is normally much depleted as term approaches. The onset of labor is postponed thus prolonging pregnancy.

Instead of injecting progesterone, if one induces ovulation in pregnant rabbits near term so that fresh active corpora lutea are present at full term, emptying of the uterus also fails to occur at the usual time. The fetuses are retained within the uterus as long as the new corpora lutea remain functional, and then are cast out. Since the life span of corpora lutea in the rabbit is sixteen days, the time of onset of labor would be calculated to occur at the end of the sixteen-day period. Observation shows this to be the case. Although pregnancy is prolonged, the gestation period is not altered in totally irregular fashion but follows a definite pattern, for the time of termination of pregnancy still coincides with the termination of the life span of the corpora lutea. Thus the superimposing of a new ovulation cycle upon pregnancy in rabbits, reveals the close relation between the duration of pregnancy and the duration or rhythm of the sexual cycle.

How long past term the fetuses can survive when parturition is inhibited experimentally is readily determined in rabbits. For three days past term or until the thirty-sixth day, the fetuses continue to grow until the size, weight, and conspicuous covering of hair correspond to that of newborn rabbits three days after birth. Intra-uterine death occurred on the fourth day past term; i.e., at thirty-six days, although emptying of the uterus failed to occur until five days later; i.e., the forty-first day, when there was marked retrogression of the corpora lutea. It is evident that these findings lend no support to the view that the onset of labor is caused by changes in the fetus, senility of the placenta, or mechanical distention of the uterus.

In brief, excessive development of the fetus in these experiments results from changes induced in the maternal organism, which in turn alter the timing mechanism that regulates the duration of gestation. Conversely, postmature fetuses of excessive size are in themselves evidence of defect or injury of the normal mechanism controlling the onset of labor.

DR. WILLIAM J. DIECKMANN.—The authors have noted some parallelism between the size of the baby and the size of the mother, but the correlation of fetal size to stature of the father is much better, as evidenced by veterinarian studies.

Dr. Koff mentioned the use of the x-ray in determining the size of the fetus and pelvis. Unfortunately the majority of the babies are still delivered in places where the special equipment for fetal and pelvic roentgenometry is lacking. The Ahlfeld or MacDonald measurements enable the experienced doctor to determine the size of the baby with considerable accuracy. Instead of guessing the weight of the baby, I suggest that these methods be taught and used.

DR. JOHN A. C. BUSBY.—I understood Dr. Koff to say that the largest baby, born alive, of which they had found any record was slightly over 15 pounds. In view of this fact I think it would be of interest to report a baby, born alive, last week at the West Suburban Hospital that weighed 16¼ pounds. This baby is still alive and doing well.

DR. PAUL H. VAN VERST.—As far as I know, a certified scale was used in the case that Dr. Busby referred to. The baby weighed 16 pounds, 3 ounces. The mother was a multipara weighing over 200 pounds before she became pregnant and about 245 pounds at the time of delivery. She had given birth previously to two large children, the largest weighing over 11 pounds. The previous pregnancy had been terminated by version and extraction because of inertia of the uterus after complete dilatation of the cervix. Similarly this time the patient developed inertia after complete dilatation had occurred rather rapidly. The attending physician called a consultant, and they again decided to do a version and extraction, which was rather

Medical induction of labor, particularly when the pregnancy is prolonged, is frequently successful. The use of Voorhees' bag in artificial rupture of membranes is not recommended, since these methods increase the incidence of infection and place the mother in great danger should more radical methods of procedure be necessary to effect delivery. It should here be stressed that induction of labor is not justifiable merely because the pregnancy has been prolonged beyond 294 days. It is only when the fetus seems excessively developed that immediate delivery should be contemplated. As a matter of fact, only one case of excessive development of the fetus occurs in every 25 pregnancies that have been prolonged beyond 294 days.

#### SUMMARY

Among 20,219 births at the Chicago Lying-in Hospital 0.94 per cent of the infants weighed more than 4,500 gm.

The average length of gestation calculated from the first day of the last menstrual period was 288 days for these infants.

The size of the fetus is largely dependent on the length of gestation, but size of the parents, multiparity, advancing age, or diabetes in the mother may be contributing factors in producing excessive development.

Labor presents a greater hazard for both mother and offspring when overdevelopment of the fetus has occurred.

The necessity for operative interference is increased and the incidence of toxemia, of post-partum hemorrhage, of maternal morbidity, and of fetal mortality is definitely higher than when the fetus is of smaller size.

Accurate estimation of fetal size prior to delivery with consequent modification of the technique employed will decrease maternal complications and fetal mortality.

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#### DISCUSSION

DR. FRANKLIN F. SNYDER.—The chief factor responsible for this abnormality of the fetus has been traced to a defect in the mechanism of labor, namely, postpone-



# THE FACTOR OF ANESTHESIA IN THE PATHOGENESIS OF ASPHYXIA NEONATORUM\*

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THE problem of respiratory failure in the newborn is open to a new experimental approach as a result of recent findings regarding the intrauterine origin of respiration.<sup>1, 2</sup> Since active respiratory movements occur throughout a large part of intrauterine life, the failure of respiration at birth must be regarded as the suppression of previous activity rather than the failure of some new mechanism to come into operation.

Investigation of the cause of depression or abolition of intrauterine respiratory movements has revealed three different types of fetal apnea, namely, acapnic, anoxemic, and anesthetic. Of these, the acapnic and anoxemic types of apnea have been described at length in a previous paper.<sup>3</sup> The present report is a description of the anesthetic type of apnea.

In our earliest experiments in which the rabbit fetus was observed directly through the uterine wall, a state of apnea was the characteristic finding. It was not immediately recognized that the anesthetics employed to permit laparotomy masked the normal state of activity of the fetal respiratory system. In the course of these experiments, spontaneous gasps occurred, especially when anesthesia was light. It was decided to eliminate anesthetics entirely. The technique was modified so that laparotomy could be done without resorting to narcosis. The spinal cord was sectioned in the lumbar region resulting in anesthesia of the lower abdominal area. Experiments carried out with this technique disclosed the error introduced by narcosis in the previous work and at the same time revealed the intrauterine origin of respiration. Intrauterine respiratory movements could be kept under observation for periods lasting many hours. Factors modifying the degree of activity of the fetal respiratory system were thus brought within range of experimental analysis. Starting with fetuses which were breathing at a regular rate, we were enabled now to return to the problem of the effect of anesthetics upon the fetal respiratory system and to evaluate the depressant action of various narcotic agents.<sup>4</sup>

## METHOD AND MATERIAL

In a typical experiment, laparotomy was carried out beneath the surface of a bath of warm Ringer's solution and the gravid uterus was brought into view. In order to preserve normal circulation, care was taken to avoid exposure of the uterus to the air and to prevent mechanical stimulation. Through the thin uterine wall of the rabbit, the intrauterine respiratory movements of the fetuses were clearly ob-

\*Presented at a meeting of the New York Obstetrical Society, February 8, 1938.

difficult, taking about thirty-five minutes. They had a little difficulty in resuscitation, but at the present time, a week after delivery, the baby is doing very nicely. The mother immediately after delivery developed atony of the uterus with severe hemorrhage. Manual removal of the placenta was done, but bleeding continued until the uterus was packed. The mother is also now doing very well. I believe a case report will be made by the attending physicians, Drs. C. N. Vetten and J. H. Skiles.

DR. ROBERT M. GRIER.—The biggest baby we ever had at the Evanston Hospital weighed one ounce less than 14 pounds. The mother was a para iv, and she was delivered without a tear. This woman was a clinic patient and weighed 160 pounds at the start of pregnancy and the day of delivery she weighed 160 pounds, having made no gain during pregnancy.

DR. EDWARD ALLEN.—Diabetic patients have large babies. Many such babies die intrapartum or intrapuerperium, not from postmaturity or obstetric trauma or over-size, but from some other outside factor.

DR. EDWARD L. CORNELL.—For the past ten years I have tried to obtain a definition of postmaturity that will hold water. If you mean by the mature baby, one delivered after 294 days, I can cite you a case of a baby delivered after 365 days which weighed less than seven pounds. If you judge postmaturity by weight, I can cite a case of a 46-year-old primipara who went 280 days, the baby was dead and weighed 13 pounds and seven ounces, without the brains or body fluid. Postmaturity cannot be judged by the weight of the baby nor by the number of weeks the mother delivers after the last menstrual period.

I think x-ray examinations do prove of value in judging disproportion. You may have a very large baby and disproportion. If these patients are given a reasonable test of labor with no progress, I think the thing to do is to deliver from above without waiting to get into difficulty. Again, if you take the relation of the size of the patient to the size of the baby as a criterion of postmaturity, I can cite you a case delivered in the old Chicago Lying-in Hospital where the baby weighed 13 pounds and 11 ounces and the mother weighed over 300 pounds.

I would not like to see a paper like this go out to the general practitioner if you base postmaturity on the number of days after the last menstrual period until delivery. If we could know the date when the patient became pregnant, then we would have something on which to base our calculations.

DR. KOFF (closing).—We agree with Dr. Dieckmann that there may be some relationship between the size of the father and that of the baby, but in a study such as this we could obtain no consistent information with respect to the size of the father.

The case described by Drs. Busby and VanVerst of the 16 pound 3 ounce baby born alive is unusually interesting, and should be reported. As far as we can determine there is no record of any infant born alive weighing more than fifteen pounds. The successful outcome should be considered a testimonial to the skill of the obstetrician, particularly since the method of delivery is by version and extraction.

We are in accordance with Dr. Cornell concerning the ambiguity of the term, postmaturity. For that very reason, we have attempted to use the term only in relationship to the duration of pregnancy. That is, when pregnancy has lasted 294 days or more. However, we wish to correct the impression that the subject of this presentation deals with prolonged pregnancy. The main purpose of this study is to point out that excessively developed fetuses frequently produce serious dystocia which results in an unusually high fetal and maternal mortality. Moreover, we feel that if a diagnosis of an abnormally large fetus can be made before the onset of labor, this mortality could undoubtedly be reduced.

It is apparent that there is some relationship between large fetuses and prolonged pregnancy. However, generally speaking, in every hundred cases of prolonged pregnancy (294 days or more), there are only four instances of excessively developed fetuses. On this basis we could hardly advocate induction of labor for prolonged pregnancy alone. On the other hand, when the fetus seems abnormally large and when the pregnancy has proceeded beyond the 294 days, it would appear to us that medical induction of labor is then indicated, particularly since in this type of case there is a 3 per cent fetal mortality prior to the onset of labor.

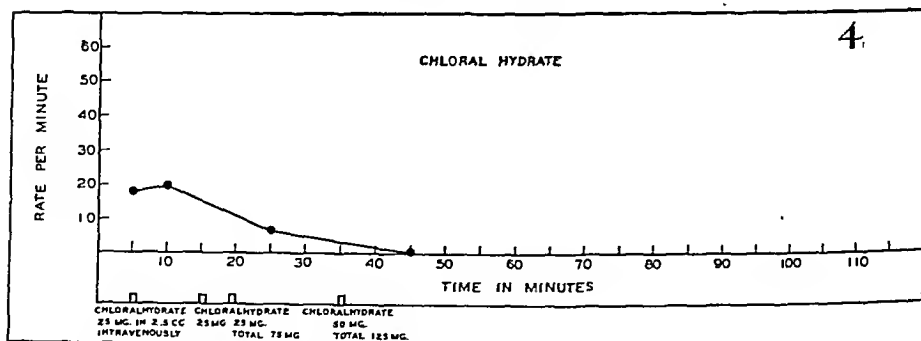
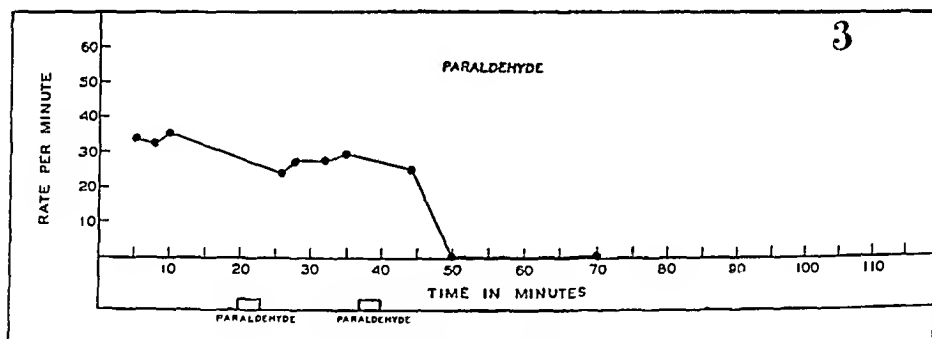
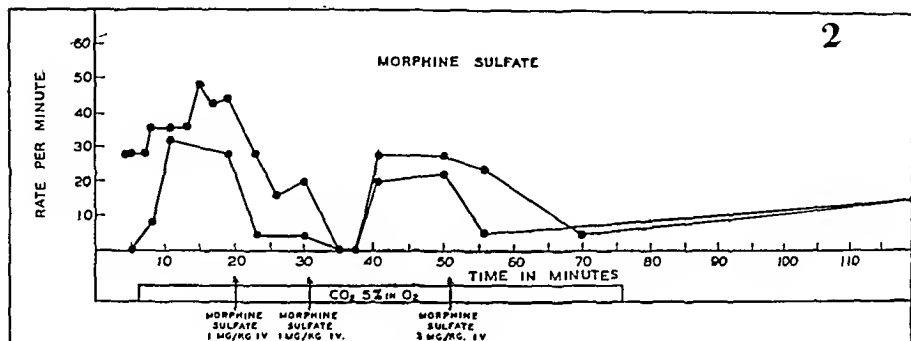
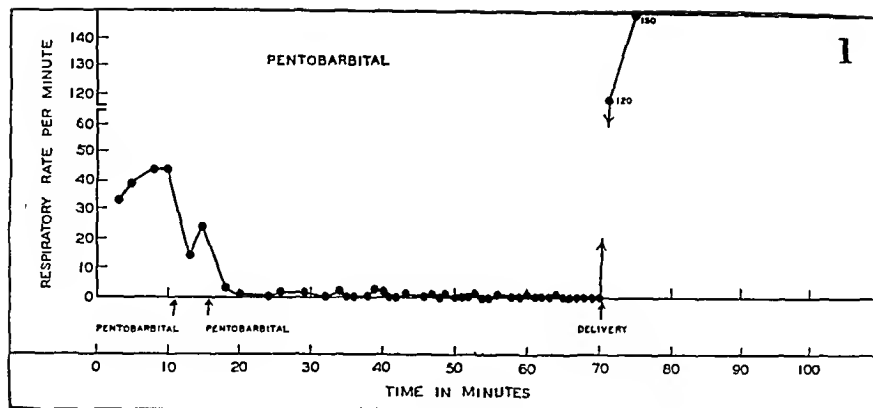


Fig. 1.—1, Pentobarbital sodium 10 mg. per kg. intravenously at each injection. Mother showed little effect; reflexes active. 2, Morphine sulfate 1 mg. per kg. intravenously at each of two injections; 3 mg. per kg. at third injection. Mother showed little effect; reflexes active. Carbon dioxide 5 per cent and oxygen 95 per cent simultaneously administered in several experiments, failed to counteract the depression of the intrauterine respiration. 3, Paraldehyde 0.25 c.c. per kg. intravenously at each injection administered in 7 per cent solution. Mother awake, but depressed; reflexes present. 4, Chloral hydrate 8 mg. per kg. intravenously in 1 per cent solution at each of 3 injections; 16 mg. per kg. at fourth injection. Mother awake, but depressed; reflexes present.

\*The graphs illustrate the effect of anesthetics upon the fetus, as determined by changes in the rate of intrauterine respiration. The effect upon the mother at the time when fetal depression set in, is given in the following legends.

served. The respiratory rate of various fetuses in the litter was recorded at repeated intervals, first during a control period and later during the experimental period following administration of a given anesthetic agent. At the same time the degree of anesthesia of the maternal animal was noted. Fetuses were delivered at various intervals in order to determine the respiratory response associated with birth. Non-volatile anesthetics were injected in solution slowly into an ear vein of the mother. Volatile anesthetics, except ether, were administered by tracheal cannula or by passage through a chamber sealed about the head of the animal. A continuous flow of the gas mixture was maintained from a Douglas bag of 100 liters capacity.

Rabbits at full term (32 days) were used throughout this work. Labor was inhibited by the injection of 1 c.c. of antuitrin-S (Parke, Davis & Co. extract of urine of pregnancy) one week before term.

Anesthesia of the lower abdomen for laparotomy was obtained by section of the spinal cord in the lumbar region.

The material upon which the present observations are based is summarized in Table I.

TABLE I. EFFECT OF ANESTHETICS UPON FETAL RESPIRATION

ANESTHETIC	APPROXIMATE DOSE	NUMBER OF ANIMALS	NUMBER OF FETUSES	SURGICAL ANESTHESIA OF MOTHER	SUPPRESSION OF INTRA-UTERINE RESPIRATION OF FETUS
Pentobarbital sodium	20 mg./kg.	9	27	0	+
Morphine sulfate	5 mg./kg.	4	16	0	+
Paraldehyde	250 mg./kg.	3	5	0	+
Chloral hydrate	25 mg./kg.	2	15	0	+
Ether, open drop technique		3	8	0	+
Nitrous oxide 90% + oxygen 10%		3	10	0	+
Nitrous oxide 85% + oxygen 15%		4	15	0	0
Cyclopropane 30% + oxygen 70%		9	32	+	0

## OBSERVATIONS

The present observations constitute a general survey of representative anesthetics belonging to both the volatile and nonvolatile groups. The effect of these agents upon fetal respiratory movements was determined and correlated with the depth of maternal narcosis. The amount of anesthetic was increased gradually in order to determine the point at which depression of fetal respiration occurred. The ultimate aim was to find out whether or not deep surgical anesthesia could be obtained without interruption of fetal breathing.

*Nonvolatile Anesthetics.*—The nonvolatile anesthetics selected for trial were pentobarbital sodium, paraldehyde, chloral hydrate, and morphine sulfate (Fig. 1). It was uniformly observed with all of these substances following intravenous administration to the mother that fetal respiratory movements were markedly depressed or completely abolished at a level of dosage well below that required to anesthetize the mother. The maternal animal remained wide awake, responsive to external stimuli and, in marked contrast to the fetus, maintained normal respiration.

The effect upon the fetus was evident within a few minutes following the injection of the mother. Under the influence of narcosis, the fetal respiratory movements may remain suppressed for hours, interrupted only occasionally by a feeble respiratory effort.

Despite the prolonged apnea thus induced, delivery of the fetus from the uterus was promptly followed after a minimal depressant dose of anesthetic, by resumption of active respiratory movements. This indicates that the fetal respiratory system during intrauterine life is extremely sensitive to the depressant action of narcotics, but does not necessarily suffer irreversible damage. Although respiration returns following delivery and often approaches normal, evidence of narcosis is manifested by the inactivity, sluggish movements, and flaccid state of the newborn.

*Volatile Anesthetics.*—Of the volatile anesthetics, ether, nitrous oxide, and cyclopropane were chosen for study (Fig. 2).

When the fetuses were kept under continuous observation during the administration of open ether by the drop technique, it was found that fetal respiratory activity was gradually depressed and finally was abolished. Regular fetal respiration could not be maintained at the level of surgical anesthesia in the mother. If ether administration was terminated and the maternal animal allowed to awaken, fetal respiration often reappeared following elimination of the anesthetic.

In the experiments with nitrous oxide the results were strikingly influenced by the amount of oxygen available. Nitrous oxide 90 per cent with 10 per cent oxygen rapidly suppressed fetal respiration, although the maternal animal showed little evidence of anesthesia. In view of the depressant action of anoxemia alone,<sup>3</sup> it was decided to test a mixture containing a greater proportion of oxygen, namely, nitrous oxide 85 per cent with 15 per cent oxygen. This latter mixture was found to have no depressant action upon the fetus even though administered continuously over a period of forty minutes. The striking difference in the effect of these two mixtures is best explained by taking into account the relatively great difference in oxygen tension in contrast to the small change in the proportion of nitrous oxide.

The experiments with cyclopropane demonstrate that deep surgical anesthesia of the mother can be reached and maintained without interruption of intrauterine respiration. Deep anesthesia of the mother with complete loss of consciousness and disappearance of the corneal reflex persisted throughout periods of administration of the anesthetic, lasting as long as half an hour. During this time fetal respiratory movements continued uninterruptedly at a regular rate and normal depth. In many instances the rate actually increased above the pre-anesthetic level. After delivery the fetuses survived without complication, and showed none of the striking signs of narcosis, such as were previously noted in fetuses subjected to the nonvolatile anesthetics.

## DISCUSSION

The fetal respiratory system during intrauterine life is peculiarly sensitive to narcosis, and the reaction to a particular anesthetic cannot be predicted from the response of the maternal animal. This special physiology of the fetus which has come to light prompts a re-examination of the anesthetics used in obstetrics, with special reference to their effect upon the fetus within the uterus. There is now available for such investigation a technique which in previous studies has aided in the elucidation of the normal physiologic regulation of intrauterine respiration.

Examination of the nonvolatile anesthetics revealed a striking depressant action upon intrauterine respiration which had not been anticipated from mere observation of the fetus after delivery or from the respiratory response of the maternal animal. Depressant effects upon the fetus are clearly revealed by this method, which might be overlooked under the usual conditions of clinical observation based upon the reaction of the mother and newborn.<sup>4, 5</sup> Intrauterine respiration is a sensitive

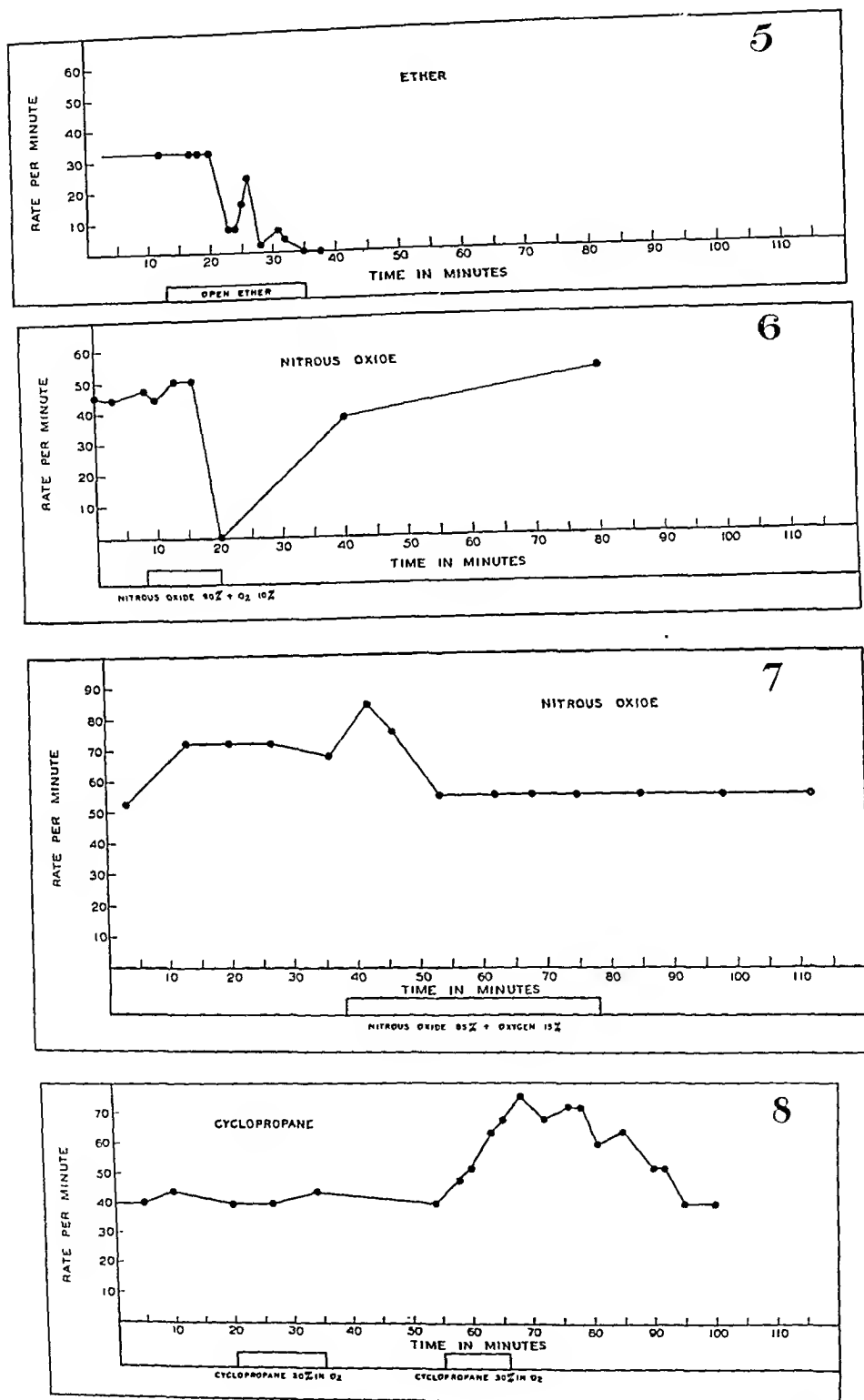


Fig. 2.—5, Ether by drop method. Gradual depression of fetal respiration which persisted in this instance after mother awakened from anesthesia. 6, Nitrous oxide 90 per cent, oxygen 10 per cent. Mother depressed; corneal reflex present. 7, Nitrous oxide 85 per cent, oxygen 15 per cent. Mother awake; reflexes active. 8, Cyclopropane 30 per cent, oxygen 70 per cent. Mother fully anesthetized; corneal reflex lost. Deep surgical anesthesia of mother without interruption of fetal breathing.

4. Because of the peculiar sensitivity of the fetal respiratory system to depression by anesthetics, the factor of anesthesia must be regarded as an important one in the pathogenesis of respiratory failure at birth.

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## CERTAIN LABORATORY FINDINGS AND INTERPRETATIONS IN ECLAMPSIA

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IN CONSIDERING laboratory tests in eclampsia, an incomplete conception of any of several factors may lead to erroneous conclusions. In interpretation, at least three questions must be borne in mind. First, what do we expect of the test; second, what are the vitiating or modifying factors which may complicate the final result; and third, what do the results mean? I can make no pretense of bringing a complete conception to the interpretation of biochemical observations. However it is not out of place to present the results of some tests in a fairly large series of eclamptic patients and to attempt to explain some of these results.

Several writers have concluded that renal function tests are of no value in toxemia of pregnancy, either because the tests have no value in predicting the later development of toxemia, or because they give normal results in toxemia. It is apparently assumed that the toxemia is either a manifestation of, or is caused by, renal deficiency. In a very recent paper, McPhail<sup>1</sup> writes, "It is believed that toxemia will not develop if no impairment of renal function exists." This, probably unfortunately, is widely believed. Many writers, however, do not accept renal insufficiency or deficiency as a cause of toxemia of pregnancy. Too much is expected of the function tests if it is thought that they may serve to predict toxemia.

As for factors modifying the tests, one might again cite the renal function measurements. The restriction of salt, commonly practiced in the treatment of toxemia, will at once reduce by nearly one-fourth the significant figures in the attainable specific gravity.<sup>2</sup> Or again, a tendency to oliguria is common in toxemia; in oliguria the glomerular filtration is apparently reduced,<sup>3</sup> and therefore most, if not all, excretion tests are modified. For instance, in oliguria the calculation of standard urea clearances gives grossly erroneous results.<sup>4, 5</sup> Yet there

indicator which can detect the earliest effect of narcosis and permits evaluation of the extent to which a particular narcotic affects the fetus. The degree of respiratory depression may be expressed in a roughly quantitative way in terms of change in rate of fetal respiratory movements. The changes in rate were of such magnitude that conclusions could be based upon them, even though the volume changes could not be measured quantitatively.

Turning to the volatile anesthetics, experiments with ether supported the previous findings with nonvolatile agents, namely, that the fetal respiratory movements were suppressed by the time surgical anesthesia of the maternal animal was reached. In the case of nitrous oxide it was found that a high concentration of the anesthetic substance did not in itself interfere with respiration of the fetus. It was only when anoxemia was superimposed that the gas mixture, i.e., 90 per cent nitrous oxide with 10 per cent oxygen, became depressant. These mixtures likewise failed to produce surgical anesthesia of the mother without first causing abolition of fetal respiration.

Cyclopropane was selected for trial because of its high anesthetic potency, which property permits the admixture of a large proportion of oxygen, 70 per cent oxygen and 30 per cent cyclopropane being used. This mixture resulted in full surgical anesthesia of the mother and at the same time provided an abundant supply of oxygen. The results with this anesthetic agent demonstrate that one important objective of obstetric anesthesia is not beyond reach, namely, the production of full surgical anesthesia of the mother without interruption of fetal respiration.

Failure of the respiratory system to function following delivery may now be viewed in the light of factors found to be depressant to fetal respiration. Three such factors have been isolated and analyzed separately, anesthesia, anoxemia, and acapnia. Of these three possibilities, the two former, namely, anesthesia and anoxemia stand out pre-eminently in any attempt to explain the etiology of functional injury of the fetal respiratory mechanism. Acapnic depression, as observed in previous experiments, has been so readily reversible that there is little ground to attribute to acapnia a significant rôle in the production of permanent injury. The demonstration of the special sensitivity of the fetal respiratory system to anesthetics and anoxemia establishes the close relation of these two factors to irreversible failure of respiration.

#### SUMMARY

1. The problem of obstetric anesthesia has been approached by a new method, based upon the direct observation of intrauterine respiratory movements in animals.

2. Most anesthetics of both nonvolatile and volatile type suppress intrauterine respiration long before surgical anesthesia is reached in the mother.

3. The result with cyclopropane illustrates the attainment of one important objective of obstetric anesthesia, namely, the production of full surgical anesthesia of the mother without interruption of fetal respiration.



with renal impairment as shown by lowered urea clearances and often by nitrogenous retention. In the first 2 series, the blood uric acid showed no definite relation to the nonprotein nitrogen, except that in most cases the uric acid was less than 11 per cent of the nonprotein nitrogen. The low coefficients of correlation, given in Table I, merely emphasize the variability of the blood uric acid levels. The higher, and significant, correlation coefficient in the patients with renal impairment indicates that the level of blood nonprotein nitrogen should be considered when assessing the blood uric acid level, especially if the nonprotein nitrogen is somewhat elevated. Again, in this series, the ratio is usually less than 11 per cent. The statistical data are summarized in Table I. The frequency distributions of the ratios are shown in Fig. 1.

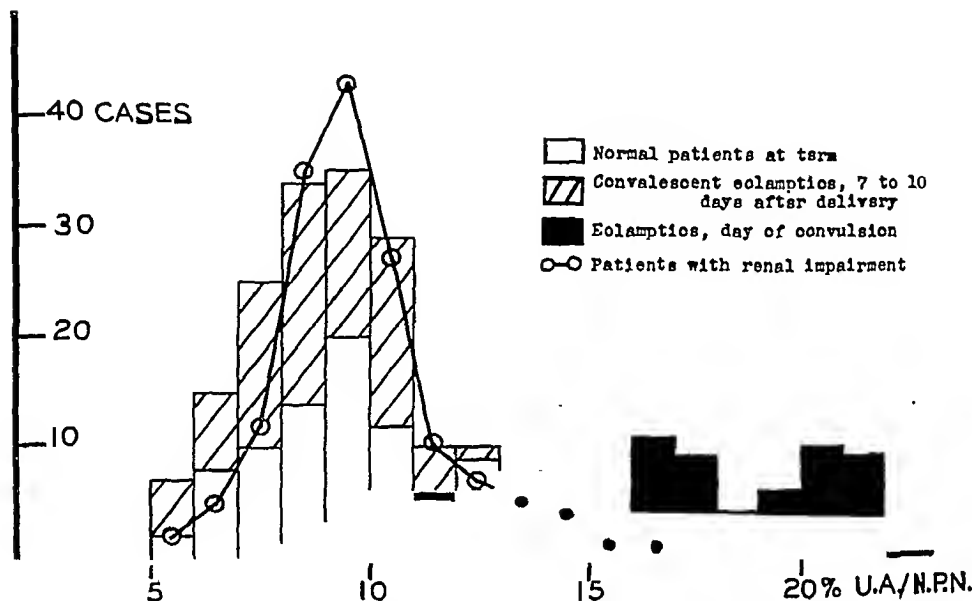


Fig. 1.—The frequency distribution of uric acid/nonprotein nitrogen ratios in the blood of eclamptic and control patients. Note that eclamptic patients show ratios characteristically above 10 per cent, while patients in the three control series show ratios usually less than 10 per cent.

Roughly then, we might take the normal proportion of uric acid to nonprotein nitrogen as about one-tenth. Accepting 10 per cent as the normal uric acid nonprotein nitrogen ratio, a blood uric acid of 4.0 mg. per cent would be of more serious import in a pre-eclamptic patient whose nonprotein nitrogen was 20 than in one whose nonprotein nitrogen was 40 mg. per cent. It is suggested that this ratio is of more significance than the absolute level of the blood uric acid. In the present series 13 of 73 eclamptic patients had blood uric acids of less than 4.0 mg. per cent on the day of convulsion, but only 4 had uric acid/nonprotein nitrogen ratios of less

TABLE I. RELATION OF THE BLOOD URIC ACID TO THE BLOOD NONPROTEIN NITROGEN IN CONTROL SERIES

GROUP	NUMBER OF PATIENTS	MEAN RATIO OF URIC ACID/N.P.N.	STANDARD DEVIATION ( $\sigma$ )	COEFFICIENT OF CORRELATION ( $\rho$ )	PROBABLE ERROR OF $\rho$
Normal	60	0.087	0.016	0.184	0.0077
Recovered eclamptics	69	0.084	0.016	0.248	0.0054
Renal impairment	27*	0.092	0.019	0.376	0.0028

\*152 blood chemistries.

are several papers in which low urea clearances, calculated from low urine volumes, are reported and considered as valid and typical findings in eclampsia.

What do the results of the test mean? In eclampsia many, though not all, investigators report that the blood uric acid is elevated. Some believe that this means renal retention, others that it means failure of the liver to destroy its quota of uric acid. In many eclamptics the blood nonprotein nitrogen may also rise. Some interpret this as evidence of an underlying and causative renal impairment; others think that it is caused by renal damage secondary to the toxemia. Since in oliguria glomerular filtration is diminished,<sup>3</sup> the rise in nonprotein nitrogen might be attributed to this factor which may be wholly independent of any renal lesion, primary or secondary.

#### MATERIAL AND METHODS

The present study is based upon 90 cases of eclampsia occurring from Jan. 1, 1934 to date. With very few exceptions, renal function tests were done on each patient. Blood chemistry values were obtained in patients in a postabsorptive state, except when urea clearances were done.

Uric acid of the blood was determined by Folin's last method,<sup>6</sup> in the Folin-Wu filtrate.

Nonprotein nitrogen of the blood was determined by Wong's method.<sup>7</sup>

Proteinuria was detected by the sulfosalicylic acid method. If positive, quantitative measurement was made by the procedure of MacKay.<sup>7</sup>

Urinary specific gravity was determined by means of a Westphal balance.<sup>7</sup> In the earlier cases a calibrated hydrometer was used. All readings were corrected for protein content of the urine and were discarded if sugar was present.

Folhard's urine concentration test<sup>8</sup> was used. The patient was given no food or fluid for seventeen hours after a 5 P.M. supper. Urine specimens were collected at 8, 9, and 10 A.M. the following morning. The specific gravity was corrected for protein content, and disregarded whenever melituria was encountered.

Urea clearances were calculated by Van Slyke's conventional formulas.<sup>7</sup> No results are reported in the statistics for clearances calculated from volumes of less than 25 ml. per hour.

Phenolsulphonephthalein excretion was measured at 15, 30, 60, and 120 minutes after the intravenous injection of 1 ml. of the dye.

#### RESULTS AND DISCUSSION

*Blood Uric Acid.*—Stander and Cadden,<sup>9, 10</sup> as well as others, have reported that in eclampsia the blood uric acid is increased; concomitantly there is little or no increase, or only a later increase, in the other nitrogenous metabolites of the blood. High blood levels of uric acid are also found when the nonprotein nitrogen rises because of renal impairment. This suggests that absolute values for the blood uric acid may not have as much significance, in toxemia of pregnancy, as would the ratio of uric acid to some other substance or group of substances. Accordingly a study has been made of the ratio between the blood uric acid and the nonprotein nitrogen. Since different methods for either uric acid or nonprotein nitrogen do not give identical values, it must be remembered that the absolute values of the ratios reported here would change with change in methods. Furthermore, uric acid itself varies more than any other nitrogenous constituent of the blood (Folin<sup>11</sup>). Both absolute values and ratios of uric acid to nonprotein nitrogen may therefore be expected to show considerable variation.

The relation of the blood uric acid to the nonprotein nitrogen was analyzed in 3 control series: (A) In 60 normal patients at term; (B) in 69 convalescent eclamptic patients, seven to ten days post partum; (C) in 152 blood chemistries on 27 patients

this concept, suggested a ratio of 0.45 as the upper limit of normal. Many writers have reported a diminution of this ratio in pregnancy. In Table II are summarized the urea nitrogen/nonprotein nitrogen ratios found in the present series of eclamptic patients. Assuming an upper normal of 0.40 in pregnancy and 0.45 *post partum*, it is seen that many eclamptics fall outside of the normal limit. Perhaps this can be explained by the tendency to oliguria, or at least by the diminished urine volume output. The excretion of urea is essentially independent of the urine volume when the output exceeds 2 ml. per minute (2,880 ml. per twenty-four hours); at all lower volumes, the urea excretion diminishes as the volume falls. (These familiar facts are the basis for the calculation of maximal and standard urea clearances.) When the urine volume is 0.5 ml. per minute (720 ml. per twenty-four hours), the excretion of urea is half what it would be at a volume of 2 ml. per minute (2,880 ml. per twenty-four hours). The urea which is not excreted must, of course, be retained; this retention is physiologic and not dependent upon a renal deficiency. The retention of urea then increases the urea nitrogen/nonprotein nitrogen ratio in the blood, perhaps driving it above the arbitrarily chosen "normal" of 0.45.

It is probable that the urea nitrogen/nonprotein nitrogen is of little value in eclampsia, and that high values often would be misleading if interpreted to mean renal impairment.

*Phenolsulphonaphthalein*.—Many of the eclamptics, as Table II demonstrates, seemed to excrete subnormal amounts of phenolsulphonaphthalein. According to Stander<sup>13</sup> ureteral dilatation, found in about 85 per cent of pregnant patients, may become so extreme as to increase the volume capacity of the ureter to as much as 60 ml., twice the average volume output of urine per kidney per hour. While the kidney may excrete normal amounts of the dye, there will be a long lag before the excreted dye reaches the bladder. An *ante-partum* factor which magnifies the apparent reduction in dye excretion is the usual low volume of urine. If it were not for diffusion and peristalsis in the ureters, the entire two-hour excretion of dye might be retained within the ureters in many cases. With the *post-partum* diuresis, the stagnant urine in the ureters is swept out more rapidly than *ante partum*, thus accounting for the larger proportion of patients showing apparently normal excretions after delivery.

We have discarded this test as worthless in the toxemias of pregnancy.

*Urea Clearance*.—There is some disagreement as to the effect, if any, of normal pregnancy upon the urea clearance. Some writers, as Nice,<sup>14</sup> report that the clearance progressively increases as pregnancy progresses. Others, as Cantarow and Ricchiuti,<sup>15</sup> state that the clearance progressively decreases. In a previous paper<sup>16</sup> I have reviewed the literature and found that in 188 normal cases, published by 9 authors, the urea clearance averaged 101 per cent. The range was 28 to 286 per cent. However, the range is given by extreme values which represent single determinations. If perhaps half a dozen of the 188 cases be thrown out as too high or too low, the range would become the familiar one seen out of pregnancy. Dieckmann,<sup>17</sup> for instance, reports his own clearance as varying from 45 to 170 per cent; my own range agrees closely with this.

We conclude, therefore, that the urea clearance is unchanged in normal pregnancy. Here, as out of pregnancy, a low clearance should be checked to determine whether the low value is a normal variation or a constantly depressed level.

As Table II shows, the urea clearance in eclampsia is usually normal. Only 3 *ante-partum* and 2 *post-partum* patients (total 3 patients) of the 72 eclamptic patients who had urea clearances, showed clearances of less than 70 per cent. A one- and four-year follow-up of 2 of these patients revealed persistent hypertension, proteinuria, and constantly low urea clearances and specific gravity. The third patient had an acute pyelonephritis with her eclampsia, and within a year had returned slowly to a normal renal functional level as indicated by the urea clearance. Forty-one eclamptic patients have been followed up for periods ranging from one to five years after the eclampsia. Only 3 of these had subnormal clearances at the last, or any, observation. Two of the 3 were the patients mentioned above,

than 10 per cent. In Fig. 1, it may be readily seen that the uric acid/nonprotein nitrogen ratio is characteristically above 10 per cent in eclampsia.

In passing, it might be worth while to note that about half of the nonconvulsive toxemia patients observed have had elevated uric acid/nonprotein nitrogen ratios (mean 0.109,  $\sigma = 0.034$ ). It is before the outbreak of convulsions, of course, that laboratory tests of possible premonitory significance are of the most value.

*Urinary Specific Gravity.*—Alving and Van Slyke<sup>2</sup> found that about one-fourth of the significant specific gravity of the urine was given by chloride, and that another one-fourth was attributable to urea. Chloride and urea excretion vary directly with the dietary intake of chlorides and protein, respectively. Since salt is very often, and protein sometimes, restricted in the treatment of toxemia, one might expect the urinary specific gravity in toxemia to fall short of levels otherwise attainable. Low urinary specific gravities, in eclamptic patients who have been under such dietary restrictions, cannot be interpreted as evidence of renal impairment. Furthermore the presence of edema makes effective restriction of water all but impossible. For even if water is not taken by mouth during a concentration test, the urine may still be diluted by the discharge of edema fluid.

In the present series of eclamptic patients, more than half failed to attain a specific gravity of 1.023 or higher as shown in Table II. To emphasize the dietary factor in this test, it is interesting to note that in the 33 patients on whom the concentration test was done *ante partum*, all who failed to concentrate to 1.023 or higher, had had prenatal care. Of those giving a "normal" urinary specific gravity, half had no prenatal care. In a few eclamptic patients and in many nonconvulsive toxemias, we have observed that the attainable specific gravity is highest at the time when the patient is admitted to the hospital. Under treatment, with the restriction of salt, the urinary specific gravities seen in the concentration tests, and in the morning urines, progressively decrease.

In brief, then, low urinary specific gravities in eclampsia mean little or nothing so far as the measurement of renal function, or of prognosis, is concerned.

*Urea N/Nonprotein Nitrogen Ratio.*—The nonprotein nitrogen of the blood is made up of many substances, some of which, chiefly urea, are excreted by the kidney, and some of which are not excreted. If there should be an impairment in the kidney's excretory function, the fraction of the blood nonprotein nitrogen which would be affected would be first and chiefly the urea nitrogen. Since the "normal" blood nonprotein nitrogen varies considerably, the ratio of urea nitrogen to nonprotein nitrogen would be a more sensitive indicator of the disturbed renal function than would the absolute level of either. Mosenthal and Hiller,<sup>12</sup> who advanced

TABLE II. RENAL FUNCTION TESTS IN ECLAMPSIA

RENAL FUNCTION TEST	NUMBER OF CASES	MEAN	STANDARD DEVIATION ( $\sigma$ )	LOWER LIMIT OF NORMAL	PERCENTAGE OF CASES IN NORMAL RANGE
Urinary specific gravity					
<i>Ante partum</i>	37	1.022	0.0057	1.023	46
Puerperium	82	1.020	0.0056	1.023	45
Urea N/nonprotein nitrogen					
<i>Ante partum</i>	25	0.407	0.088	0.40*	52
Puerperium	58	0.406	0.087	0.45*	73
Two-hour excretion of phenol-sulphonephthalein					
<i>Ante partum</i>	18	59.2	8.20	60	56
Puerperium	29	66.9	8.75	60	76
Urea clearance					
<i>Ante partum</i>	19	96.7	19.7	70	85
Puerperium	64	96.8	15.3	70	98
1 year or more <i>post partum</i>	41	97.1	17.4	70	93

\*Upper limit of normal.

It will be seen that in the equations for maximal and standard urea clearances the blood urea is the divisor. Therefore *errors in the determination* of blood urea will raise or lower the calculated clearance. *Actual variations* in the blood urea will not have this effect upon the clearance. The higher the blood urea, the more urea is filtered; of the filtered urea a constant *proportion* is reabsorbed (with correction for urine volume, discussed above). The clearance is essentially independent of the blood level of urea. Therefore the statement that edema affects the urea clearance by diluting the urea of the blood (which is in equilibrium in all of body water) cannot be accepted. Nor can another investigator's statement<sup>20</sup> be accepted that the urea clearance varies with the binding or release of urea by the "tissues" (unless the "tissues" are limited to the renal tubular epithelium).

In some cases of edema, there may be an oligemia (hemoconcentration) of sufficiently marked degree to diminish the renal blood flow. In such cases the glomerular filtration would probably be lowered, and extrarenally caused diminution in the urea clearance would result. In many such cases, the concomitant oliguria would point to the fallacy of calculating the standard urea clearance.

#### SUMMARY AND CONCLUSIONS

An analysis of some laboratory findings in 90 cases of eclampsia is presented.

In the interpretation of laboratory tests, certain modifying factors must be borne in mind. Some of these tests and their modifying factors include the following.

*Blood Uric Acid.*—The absolute level is often elevated in eclampsia. More generally, the ratio of uric acid to nonprotein nitrogen is increased. The upper normal ratio, by methods used here, is about 10 per cent.

*Urinary Specific Gravity.*—The attainable concentration of the urine is markedly reduced, not by eclampsia usually, but by the prophylaxis and treatment of the disease.

*Urea N/Nonprotein Nitrogen.*—This ratio varies with the urine volume output and tends to decrease in normal pregnancy. As a measure of renal function, it is nonspecific and, in toxemia especially, is unreliable.

*Phenolsulphonephthalein.*—In eclampsia and in pregnancy generally ureteral dilatation may be so marked that in spite of a normal renal excretion of dye, the test seems to give subnormal results. The dye may be excreted, but stagnating in the ureters, is not available for analysis.

*Urea Clearance.*—In my opinion, the urea clearance is unaffected in pregnancy and is normal in eclampsia, unless there is a concomitant renal disease. Urea clearances, if calculated as standard clearances, are grossly erroneous when the urine volume output falls below about 0.35 ml. per minute. The calculated standard clearance, as well as the maximal clearance, is independent of the urine volume output (above 0.35 ml./min.). It is also independent of the blood urea and of factors influencing the blood urea, such as tissue binding or tissue release of urea. When marked hemoconcentration occurs, the clearance may be low because of this extrarenal factor.

I am indebted to Drs. S. A. Cosgrove, J. F. Norton, and E. G. Waters, from whose services practically all of these patients were drawn, for reading and criticizing the typescript.

who had persistent hypertension, proteinuria and diminished renal function. The third patient's clearance, in a single determination, was 68 per cent (abnormal?).

I am not in agreement with several statements made in certain publications dealing with the urea clearance in pregnancy for reasons to be described. The mechanism of urea excretion, as shown in detail by Chasis<sup>18</sup> as well as by other writers with different methods, is as follows. The glomeruli of the ideal normal adult filter from the plasma a fluid volume averaging 122 ml. per minute. This ultrafiltrate is essentially identical in composition with protein-free plasma. It is remarkably constant in volume, whatever may be the final urine volume above a critical limit (see below). If all of the urea thus filtered were found in the final urine, the plasma urea clearance would be identical with the glomerular filtration, i.e., 122 ml. per minute. There is, however, an immediate and obligatory reabsorption of about 40 per cent of the filtered urea; if no more be reabsorbed, the plasma clearance of urea would then be about 73 ml. per minute. As a matter of fact, at all urine volumes above 2 ml. per minute, there is essentially no further reabsorption, and the whole blood clearance of urea averages 75 ml. per minute, the "100 per cent" of Van Slyke's maximal urea clearance. When the urine volume falls below 2 ml. per minute, a further reabsorption of urea occurs. Empirically, at these lower volumes, it has been found<sup>7</sup> that the urea clearance ( $UV/B$ ) follows a power curve the equation for which averages

$$UV/B = 54 \sqrt{V},$$

where  $U$  = urine urea concentration,  $V$  = volume of urine per minute, and  $B$  = whole blood urea.

Therefore the actual urea clearance,  $UV/B$ , is different at each and every urine volume below 2 ml. per minute. In order to get a *constant* which might be taken as a standard of reference, as 100 per cent, the equation is juggled, and the standard urine volume set at 1 ml. per minute, getting the form:

$$\text{Standard "Clearance"} = \frac{U \sqrt{V}}{B}$$

The result of this calculation gives what the patient's urea clearance would be if the urine volume were 1 ml. per minute. It does *not* give the actual clearance which is always  $UV/B$ . When the urine volume output falls to 0.35 ml. per minute, the urine is apparently maximally concentrated, and any further decrease in volume must be related to a parallel reversible decrease in glomerular filtration.<sup>3</sup>

Several investigators have reported low urea clearances in eclampsia; some have mentioned the fact that the clearances were done with low urine volumes.<sup>17, 19</sup> This accounts for the low clearances. For instance, in one eclamptic patient of the present series, an *ante-partum* urea clearance was done with the following result: The average minute volumes of urine were 0.182, 0.241, 1.34, and 1.86 in successive hours. The calculated standard clearances were 34, 42, 81, and 83 per cent. The first two are in error though it has been customary to calculate standard urea clearances from any urine volume below 2 ml. per minute. As mentioned above, recent work<sup>4, 5</sup> has shown that the assumption on which standard clearances are calculated does not obtain when the urine volume falls below 0.35 ml. per minute, and that such calculation gives results far lower than they actually should be. In the present series, all recorded clearances were calculated from urine volumes of more than 0.5 ml. per minute. Low clearances, such as are reported in the literature, could be calculated in many cases where the volume output of urine in the first hour or two of the test was below 25 ml. However the recorded clearances were obtained by continuing the test over a longer period until the volume of urine passed was satisfactory.

The statement has been made that the urea clearance in normal and in toxemic pregnancy is decreased because of the diminished urine volume.<sup>17</sup> So far as the actual clearance is concerned, this is true. However, in these cases, standard clearances have been calculated, and the cause assigned for low standard clearances cannot be accepted (unless the urine volume is less than 0.35 ml. per minute, in which case standard clearances must not be calculated).

into the uterus. Typical proof of this is found in our Case 7, where we find the organism introduced by an attempted delivery in the home.

*Postulate 2. Dead Tissue Must Be Present at the Time the B. Welchii Organisms Are Introduced.*—Anaerobic conditions may be established by such tissue, such as a dead fetus, but more usually other injured tissue plugging the cervix. Our Case 2 exemplifies this postulate and is typical, as an arm was prolapsed for twelve hours and plugged the cervix.

*Postulate 3. The Injured Tissue, or Pabulum, Must Remain in the Uterus for a Sufficient Length of Time for B. Welchii Incubation.*—Typical proof of this third postulate is found in Case 8, already reported by Toombs<sup>5</sup> in 1932: "The membranes ruptured two days before labor started. Labor was uneventful in the first and second stages. The placenta was retained ten hours, then removed manually. The uterine cavity and vagina were packed to check hemorrhage. The pack remained in situ for twenty-six hours. Later, the case terminated in a fatal emphysema."

*Postulate 4. Damaged Maternal Tissue Must Be Exposed to the Bacteria.*—It has been shown<sup>3</sup> that the severity of the *B. welchii* infection is usually proportional to the amount of damage done to the maternal tissues. Generalized gas sepsis has been generally reported<sup>3</sup> in cases where there were gross manipulations in the presence of Postulates 1, 2, and 3. Our Case 1, however, is a contradictory example, for notwithstanding the presence of Postulates 1, 2, and 3, there was no resultant generalized sepsis. The dead fetus had been in utero for thirty hours, but the operative manipulations were so carried out that only a little damage was done to the maternal tissues, and our patient recovered from the mild *B. welchii* infection. At the same time, it must be remembered that the most virulent types of infection have been known to follow trivial interference. Another example is Case 13, where the gross damage to the maternal tissues should have been mild, in all probability, but was converted into a grave case with sloughing of the bladder floor and a resultant vesicovaginal and rectovaginal fistula, as the result of a pressure necrosis.

In 1900, Welch<sup>6</sup> classified *B. welchii* infections in pregnancy as follows: (I) Emphysema of the fetus, (II) puerperal endometritis, (III) physometra, (IV) emphysema, and (V) puerperal gas sepsis.

In 1936, Hill,<sup>7</sup> closely following Nurnburger and Heim, classified these infections as follows: (I) Local gas gangrene, (II) physometra or gas gangrene of the uterine wall, (III) peritonitis, and (IV) bacteremia.

We shall classify them as follows: (I) Local gas gangrene, (II) emphysema of the uterine wall, and (III) gas sepsis: (A) general sepsis, and (B) metastatic gas gangrene.

#### I. LOCAL GAS GANGRENE

This class covers infections limited to either the fetus or the endometrium, or both, with or without physometra. Physometra in these cases is largely a matter of obstructed drainage and is rare when the uterus is draining well.

Falls<sup>3</sup> reported 6 cases of *B. welchii* infection with recovery. Four of these 6 were associated with physometra and 2 were apparently local infections which were free of signs and symptoms after delivery. Positive cultures were obtained from the fetus, uterus, and lochia in all of these cases. Hill<sup>7</sup> states that the majority of these cases are mild, but severe infections with hemolytic phenomena occur occasionally. Lash<sup>8</sup> states that if the process remains localized to the ovum or endometrium and is well walled off, the symptoms are very slight and the patient usually recovers, even though the organisms are found in the blood stream.

We present 6 cases in this group with no maternal deaths and one fetal death, which occurred in a twin pregnancy. Two of these cases were criminal abortions.

#### II. EMPHYSEMA OF THE UTERINE WALL WITH GAS IN THE MYOMETRIUM

It is agreed that these cases are desperate when the uterine musculature becomes involved. A fatal issue is to be expected. According to Hill,<sup>7</sup> "It is indeed difficult to understand how, once the uterine musculature becomes involved, recovery can occur without early extirpation of the uterus."

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## B. WELCHII INFECTIONS IN PREGNANCY\*

WITH A REVIEW OF THE LITERATURE AND A REPORT OF SEVENTEEN CASES

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IN 1928, Toombs and Michaelson<sup>1</sup> recalled attention to the problem of *B. welchii* infections in the puerperal state. Since then, a number of notable papers have appeared upon this subject in American and foreign literature. We propose to review this literature with particular reference to diagnosis and treatment, and to present a series of 17 cases occurring in our clinic.

## REVIEW OF LITERATURE

The sources from which one may contract a *B. welchii* infection are manifold. Usually, this organism is found in the intestinal tract of herbivorous animals, though almost any animals, and even man, may be carriers. There are many such cases reported. The synonyms for this organism are: *B. aerogenes capsulatus*, *B. phlegmonis emphysematosae*, *B. perfringens*, and *B. welchii*. The latter term will be used throughout this paper. The nature of this infection must be diagnosed or strongly suspected, before or very shortly after the onset of its symptoms and physical signs, in order that treatment may be instituted if it is to be effective.

In 1930, Wrigley<sup>2</sup> promulgated certain postulates and, with a few observations concerning his first postulate, we will proceed, in the light of subsequent research, to modify all of these:

Wrigley was unable to find the *B. welchii* in the contents of the cervical canal in early labor, nor could he find it in the lochia when the pregnancy, labor, and puerperium had been normal. Falls<sup>3</sup> found the *B. welchii* organism in the vagina in 5.5 per cent of the 270 cases examined prenatally in 1933, while Bysshe<sup>4</sup> in 1938 found five positive cultures in 222 prenatal cases examined, and one positive culture in 42 cases examined on admission to the labor room. These postulates are as follows:

Postulate 1. The Organism Must Be Introduced Into the Uterus From Without, or, in rare cases, the organism already present in the vagina or cervix must be carried

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and larger and a skiagram showed an outline of the tumor and the gas which it contained. A tympanitic tumor was punctured and fetid gas escaped, but no fluid or pus. Cultures showed *B. welchii* and an anaerobic streptococci, and culture from the uterine cavity showed the same organism. The patient passed into a state of collapse and died the fourth day after admission.

We have in our series no case of metastatic gas gangrene, although Case 14 shows the result of local damage in general sepsis where both enbital fossae had local areas of tissue necrosis following intravenous injections. Metastatic cases are probably the result of the patient's lowered resistance, where the bacilli circulating in the blood stream lodge in a tumor, or in an injury with a poor blood supply and there set up an inflammatory condition. Laboratory findings, other than smears and anaerobic cultures, will give little information concerning the type of organism with which one is dealing. Anemia is the salient feature of this disease. The white blood cell count may be as low as in cases of malaria, or it may be normal, or the total may be very high with a high polymorphonuclear count. The young cells show a reticulo-endothelial increase. The hemoglobinemia may be greater than the red blood cell count would suggest, but usually it fluctuates in keeping with the total red blood cell count. The urea nitrogen and nonprotein nitrogen of the blood will be normal in cases of local infection and in some cases of general sepsis, unless the infection is superimposed upon an existing nephritis, but uremia may develop in the course of the disease. Smears for malarial parasites should be made upon all persons who live in malarial districts. The presence of a hemoglobinuria can be detected, but we have recognized this condition only in the fatal cases. Albumin is found in varying quantities but may be absent and the presence or absence is not indicative of a severe infection. The cultures of the urine are not positive for the *B. welchii* organisms in all cases. The anaerobic stool culture is seldom positive.

Since the above laboratory findings are of no particular value in dealing with the early diagnosis of the case, the anaerobic culture of the lochia and uterine contents becomes the most important medium for diagnosis. Some authors have suggested a prophylactic dose of antitoxin when the membranes have been ruptured for some time and a foul liquor or vaginal discharge is present. We do not agree with this because there would be many an unnecessary dose of antitoxin given, if this were done routinely. We strongly advise that smears and cultures be made in such cases rather than the routine which they have suggested. The insertion of a sterile speculum into the vagina under aseptic conditions will not subject the patient to undue danger, after preparation of the external os and the cervical canal, and it is not a difficult matter to obtain the intrauterine material for aerobic and anaerobic cultures. It is our belief that there will be no increased danger to the patient by this procedure. Any necrotic and foul materials plugging the cervical os can be removed with a sponge forceps for cultures and identification at this time. If the patient has a history which would suggest a rapid course of the disease, a skiagram can be made in order to detect any early emphysema of the myometrium.

#### DIFFERENTIAL DIAGNOSIS

The physical examination does not give much information in *B. welchii* infections because the outstanding findings are a tender lower abdomen, uterus, liver, renals, and the spleen. All these may be tender in a simple case of abortion, the patient suffering from diseases which antedate the abortion. The heart cycle and pulse rate are again of no value because there are no murmurs and no irregularities of the cycle encountered in even the more advanced types.

Peritonitis is not found in the mild cases which we classify as local infections, but it is found in those patients who suffer from a general sepsis with or without emphysema and physometra. Here again the physical findings are not characteristic of the disease itself, because the patient

Uterine pain is also an outstanding feature of these cases and is vividly illustrated in Case 7, where the uterine tenderness was very marked. The actual detection of emphysema of the uterine wall is somewhat difficult as demonstrated by Case 10 of our series. One of the authors found the patient, on the day of death, with a distended abdomen and an enlarged, crepitant, boggy uterus, tender upon pressure. There was a foul lochia containing gas bubbles oozing from the vagina. No crepitation was noted in Case 8, although the uterus was large and exquisitely tender upon pressure. The uterus was removed immediately after death, and it showed a swiss cheese pattern of the cavities containing gas.

Circulatory collapse is an outstanding symptom in these cases, and is well illustrated in Case 8. The patient experienced a profound shock and recovered twenty-six hours after being packed for post-partum hemorrhage. Eighteen hours later, the patient again went into a shock from which she recovered, only to die of her sepsis two days later. Again, this phenomenon of circulatory collapse is shown well in Case 10, where the patient went into collapse two days following delivery and recovered, the blood pressure being 80/60. Another collapse occurred some six hours later, in which state she remained for four hours, then died.

Gas was demonstrated easily inside the uterine cavity and in the myometrium by a fortunate skiagram in Case 9. We have found no similar skiagram in any of the literature as far back as 1896.

Brutt and Lehmann<sup>10</sup> state that the uterus is enlarged, very sensitive to pressure, of a soft elastic consistency, and crepitation may or may not be found upon manipulation.

All of our emphysema cases were puerperal in character.

### III. GAS SEPSIS

*A. General Sepsis.*—"Gas Sepsis" was used by Welch<sup>6</sup> to designate that important group of fatal cases in which gas bubbles are found at early autopsy in the heart, other organs, and tissues. Case 9 in our emphysematous group is comparable. Before death the skiagram revealed gas in the uterine cavity, uterine muscles, peritoneal cavity, and soft tissues in general. With the continued and repeated passage of *B. welchii* into the blood stream, clinical findings of sepsis occur. This sepsis may be associated with an endometritis, emphysema, or a peritonitis.

Case 12 is a classical example of postabortal sepsis. An initial chill occurred after an attempted abortion and the patient had a high fever the following day. Nausea, vomiting, and jaundice occurred the next day. The patient began to void dark urine. The third day after the attempted abortion, the patient was jaundiced completely, had severe headaches, intense abdominal pain and was critically ill. Catheterization removed a small amount of dark coffee-colored urine which contained albumin (4+) and hemolyzed red cells. Uterine cultures were positive for *B. welchii*. The next day, the patient rapidly grew worse, with a rapid, soft pulse, dyspnea, slow shallow respirations, deepening cyanosis, restlessness, and increased jaundice to a mahogany brown. Catheterization revealed an ounce of dark, thick, viscid material. The patient passed into a moribund state and died on the seventh day after the attempted abortion. She was mentally alert until the last day, a characteristic and striking feature. This is the classical course of gas sepsis. Case 12 (1927) is a good example of a terminal anuria when the patient seemed to be recovering from a grave infection. The entire pathologic picture was predicted before death. The microscopic examination revealed a nephritis with red blood cell casts plugging the tubules.

*B. Metastatic Gas Gangrene.*—Metastatic gas gangrene is usually rare and its course is rapidly fatal, with localized pain at the site of the abscess, followed by circulatory collapse, and death. Hill<sup>7</sup> reports one case where the abscess developed in the left buttocks upon needling and the patient died before the abscess became walled. de-Sa<sup>11</sup> reports a case where a previously existing tumor of the right breast became tender and hard, with crepitation developing at its base. The patient became worse, with a high fever and intense pain in the tumor. The tumor became softer

The history of the case is most important for a differential diagnosis in any infection, but this is not easily obtained, because frequently rural patients arrive in the care of ill-informed friends and their families cannot be contacted.

The foul and discolored lochia that may be present in puerperal and abortion cases is not always due to one of those organisms classified as gas-producing bacteria, but it may be due to the anaerobic streptococci which can cause gas formation, as has been shown by some authors.<sup>12</sup> Here, again, the laboratory plays an important part and it is strongly suggested that smears be made from the lochia in such cases in order to classify the organisms present. One of the best methods for an early diagnosis of invading organisms is the intrauterine culture, placed upon aerobic and anaerobic media. It is true that some time has to elapse before the reports of such cultures are available, but treatment should be instituted to combat the organisms recognized in the smears.

The exact diagnosis of the infection is not always easy, as we have shown. The laboratory findings, with the valued assistance of the roentgen ray, are the final criteria for the diagnosis. This being true, upon admission to the hospital, the question of differential diagnosis between *B. welchii* and other infections, which give similar clinical findings, is of the greatest importance. All of us have seen patients die as a result of the *B. welchii*, and it is not the purpose of this paper to list all the changes and findings, because many writers have already described these conditions. But we do wish to emphasize some of the significant facts concerning the more severe cases, such as: a rapid, low-tension pulse, a sallow skin which is cold and clammy, and perhaps a normal temperature. The fulminating fatal types present dyspnea, cyanosis, consciousness to the last as a rule, and terminal restlessness. Rather, we wish to present the physical condition of a case which does not terminate fatally. The differential diagnosis becomes complicated in view of the multiple symptoms and physical findings.

#### TREATMENT

The treatment of this infection is varied and there is no preparation which will cure all cases. We would like to recall to you the dosage advised by Porter<sup>13</sup> for antitoxin. The unit is the amount of the unconcentrated antitoxin to neutralize 100 M.L.D. of welchii toxin, i.e., minimum lethal dose of toxin that will kill a 300 gm. pigeon.

The so-called specific treatment used in the United States is a polyvalent antitoxin serum, but all have witnessed the occasional failure of this preparation. Of course, if the condition is diagnosed early, massive doses of the antitoxin intramuscularly and intravenously are indicated and the infection will be confined within limits. When the *B. welchii* and its associated groups are recognized in the smears, a massive dose of serum should be given intramuscularly at that time, and an earlier diagnosis of these cases can be made if this procedure is followed. Likewise, if the streptococci are recognized in the smears, it is well to give 20 ml. of puerperal polyvalent antistreptococci serum in the same manner. It is the belief of the authors that many fatalities can be averted if this is done. Of course, the usual intradermal tests should have been made preceding the injections.

It seems that the number of units administered can be unlimited without injuring the patient, but the prophylactic dose of 10,000 international units is not sufficient to prevent further spread in even the local infections. The total dosage administered

may present a perforated organ. Therefore, the differential diagnosis is of great importance, positive smears and anaerobic cultures are indispensable in the early diagnosis of *B. welchii* infections.

Cyanosis is one of the common symptoms which accompany *B. welchii* infection, and it is important to differentiate between that resulting from sulfanilamide therapy or that which is seen in the later stages of eclampsia. The first sign of cyanosis is a slightly blue tint of the nails which deepens in color as the terminal state nears. A slight dusky appearance of the sclera is characteristic of all three conditions. The lips eventually become cyanotic in the moribund cases of both eclampsia and *B. welchii*, which is also the usual finding with large doses of sulfanilamide. Early edema of the lungs does not necessarily terminate fatally after the cyanosis appears, but when this condition is found, it may be the beginning of the end. There are other infections and drugs which might cause cyanosis, but the above-mentioned conditions are those encountered most often in obstetrics.

Jaundice is another finding which occurs in the more severe cases, but not in those which we have classified as local infection. Malaria is not uncommon in the South and the sclera of the eyes will be jaundiced as a result of this disease, as well as chronic infestation by certain cestodes. Of course, there may be a mixed infection with the *B. welchii*, as in Case 4, but here again, the laboratory plays a prominent part. The fulminating types of the disease which end fatally are not considered here because the bronzing of the skin is rather typical after the disease has progressed. Those different types of streptococci infections which cause destruction of the red blood cells will cause jaundice and are of importance to the obstetrician. Acute and chronic biliary diseases must not be disregarded in a jaundiced patient. However, the correct differentiation of the above conditions can be detected if a good history is available, because the jaundice accompanying a *B. welchii* infection is of short duration and deepens rapidly. This is also true when there is a calculus plugging the cystic duct.

The odor of the patient suffering from a *B. welchii* infection is not much different from that associated with typhoid. The pulse is similar in the early stages, becoming rapid and of low tension in both diseases, but it is a dicrotic pulse in typhoid fever. The patient suffering from the *B. welchii* infection has not the facies of anxiety found in the typhoid patient. The temperature is usually lower in the former disease than in the latter, and the patient suffering from a *B. welchii* infection has a cold and clammy skin in contradistinction to the hot and moist skin of the typhoid patient. Incontinence of urine and feces is a rather common finding in severe infections of *B. welchii*, with high fever, but such conditions can also result from many other causes.

Gas has not been found in the lochia of all cases but in fatal cases, only. Gas was seen in the lochia of Case 7 in the physometra group and in Case 10 in the emphysema group, but these were moribund. Gas bubbles are a rather uncommon finding in most cases, and if one waits for the presence of gas bubbles before diagnosing the condition, we believe that all efforts to save the patient will be thwarted by death.

TABLE I

	LOCAL INFECTION								GAS SEPSIS	
	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7	CASE 8		
Race	White	Colored	White	White	Colored	Colored	Colored	Colored		
Age	22	34	32	23	18	22	15	Colored	Colored	CASE 8
Para	2	10	7	0	0	2	0	0	0	38
Gestation	8 wk.	40 wk.	9 wk.	40 wk.	40 wk.	12 wk.	40 wk.	40 wk.	40 wk.	8
Membranes ruptured	48 hr.	32 hr.	48 hr.	4 hr.	6 hr.	Unknown	72 hr.	72 hr.	72 hr.	40 wk.
Total hr. labor	None	41 hr.	None	19¾ hr.	12¼ hr.	None	96¼ hr.	96¼ hr.	27½ hr.	½ hr.
Type delivery	Criminal abortion	Version	Criminal abortion	Low forceps	Midforceps	Criminal abortion	Craniotomy	Craniotomy	Spontaneous	
Temperature	98.6°-105°	99°-105°	98°-104°	98°-104°	98°-101°	98°-101°	100°-105°	100°-105°	98°-104°	
Pulse	120	80-130	76-120	74-88	84-104	74-130	98-140	98-140	86-130	
Respirations	20-22	20-30	20-26	20-22	20-22	20-24	20-26	20-26	20-22	
Blood Pressure	Not reported	100/70	98/72	120/80	130/96	110/70	150/100	150/100	Not reported	
Hospital days	7	17	6	28	19	12	1	1	4	
Gas bubbles	No	No	No	No	No	No	None on Adm.	None on Adm.	No	
Cultures	Negative	2	2	1	1	2	0	0	0	
	Positive	1	0	1	0	0	1	1	1	
Cultures	Negative	1	1	0	0	0	1	1	1	
	Positive	0	4	1	2	2	0	0	0	
Laboratory findings	R.B.C.: 3.5 Urine: Neg.	Hg.: 64-72% R.B.C.: 3.3-3.4 W.B.C.: 16,900 Urine: Casts and Alb. Malaria: Neg.	Hg.: 70% R.B.C.: 3.6 W.B.C.: 11,2 Urine: Neg. Malaria: Neg.	Hg.: 56% R.B.C.: 3.0 W.B.C.: 9.0 Urine: Neg. Malaria: Pos. Ict. index 8.	Hg.: 60-72% R.B.C.: 3.7 W.B.C.: 12.0 Urine: Neg. Malaria: Neg.	R.B.C.: 2.8-3.7 Hg.: 60-72% W.B.C.: 18.8 Urine: 10-12 Pus cells	R.B.C.: 4.3 Hg.: 80% W.B.C.: 12.0 Urine: 2+ Alb. Malaria: Neg.	R.B.C.: 1.0-3.5 W.B.C.: 36.6 Hg.: 70% Urine: Neg. Malaria: Neg.		
	None	Midwife used pin to rupture membranes	None	Tertian malaria	Toxemia. Atonic bladder. Infected epis.	Hemorrhage. Vag. packed. To hosp. 2 days later. Cervix necrotic. Mixed infection.	Attempted forceps by rural Doctor. Face presentation. Eclampsia—craniotomy. Peritonitis. Oliguria.	Manual removal of placenta. Pelvic thrombosis		
Complications	Lived	Lived	Lived	Lived	Lived	Lived	Died	Died	Died	
	Abortion	(Twins) 1 D 1 L	Abortion	Lived	Abortion	Abortion	Died	Died	Lived	
Autopsy	None	None	None	None	None	None	Yes	Yes	Yes	

depends upon the condition of the patient, and we suggest that massive doses be given twice each day for a few days, as soon as a positive culture or smear has been reported, and until the cultures in the media suggest that the organism is becoming attenuated.

After the patient is admitted to the hospital, she should be placed in strictest isolation. The importance of this procedure cannot be overemphasized, knowing that the organism has been cultured even from the delivery room and its contents. A mat soaked in bichloride of mercury solution and placed upon the threshold of the patient's room is of some value in these cases, but much less so than in those cases of other acute infections. All persons entering that room must wear sterile gowns and gloves. We insist upon all gowns, gloves, bedclothing, and articles in the room being sterilized by the fractional method before being returned to service. The importance of fractional sterilization cannot be overstressed, and if the diagnosis is made before the onset of labor, the patient should be delivered in a room equipped to handle infected cases. The room is closed from further use for a period of forty-eight hours upon discharging the patient from the hospital.

Oxytocics are important in all cases of a puerperal endometritis when administered in the proper dosage over a period of days. The usual routine of giving an ergot derivative for a few days is not of much value, because these patients suffer from an acute condition and the resultant effect is almost nil. Pituitary extract is the best drug to bring about proper contraction of the myometrium in endometritis, and we advise that 1 ml. be given every hour for four to five doses and then every two to three hours during the first twenty-four hours after the positive smear. In one case (Case 7), a combination of oxytocics was administered for seven days after the diagnosis was made, but it must be remembered that ergot and pituitrin do not have a synergistic action.

The diet and the fluid intake should be much greater than the minimum requirements for maintenance. The fluid intake and output should be carefully recorded every twelve hours, and the patient should receive at least 4,000 c.c. of fluids each day, the method of administering being dependent upon the condition of the patient. We recommend a low protein, salt-free diet because of the accompanying nephritis. Rapid destruction of tissues with an accumulation of nitrogenous products is readily shown by the resulting uremia in the severer types. We believe that vitamins have their place in the regimen and our patients receive concentrated vitamin preparations twice daily.

We strongly suggest the early digitalization of all patients until symptom-free, in order to increase diuresis, prevent circulatory collapse and slow the pulse, lest the patient should suffer from a severe infection later in the course of the disease. Massive doses of potassium citrate are administered early and continued until the patient is definitely free from her infection. Most diuretics can be used with the desired results. The mercurial preparations must not be used.

Acidosis is a rather constant finding in *B. welchii* infections. Originally, we used intravenous soda solutions for a rapid effect, but a much better and less dangerous preparation is Hartmann's solution when the  $\text{CO}_2$  combining power of the blood ranges below 45 per cent. An intravenous solution of 500 c.c. will suffice and this may be repeated as often as necessary. Large doses of soda given by mouth will assist in combating this condition. We suggest two drachms every three hours if there is no protracted emesis.

The peritoneal cavity and its organs suffer from the devastation wrought by this bacillus. Marked distention of the abdomen is present in those cases where the disease has progressed beyond that point which we classify as local infection. However, we institute deflation of the intestinal tract by the insertion of tubes from above and below. The Wangeusteen apparatus is inserted into the duodenum, left in situ as long as there is distention, and the patient is fed through the tube which is clamped for a couple of hours after the liquid meal. The colon tube is not allowed to remain in situ for more than two hours at a time because injury to the soft tissues may result. We attempt to treat peritonitis in the same manner, but we have not had good results and all such cases have terminated fatally.

The question of transfusions is of great importance. The rapid hemolysis of the red blood cells, which may occur in some cases, is too accelerated for the reticulo-

endothelial system and the loss must be replaced with transfusions. Sulfanilamide has been used successfully in some cases, but we have had no experience in its use. It does seem logical, however, that the resulting anemia will be quite a problem to combat when rapid hemolysis is taking place as a result of the infection and the necessarily massive doses of this drug. The method used in administering the blood is not of importance, but daily transfusions are strongly urged. We believe that 300 to 500 c.c. of blood will give the patient food, cell replacement, and also have a polyvalent effect upon the organisms which so frequently complicate the disease. Perhaps better results can be obtained if these daily transfusions are continued for the same period of time as that suggested in regard to the antitoxin, and we see no objection to giving the patient a transfusion twice a day if the blood is available. The red blood cell count may be lower than the hemoglobin determination would indicate, or the reverse of this condition may be true, and the supply of available blood should be used for replacement in either condition.

We would like to stress the importance of the intrauterine cultures, and to reiterate that these should be taken upon admission, if the smears are positive for *B. welchii* or any other anaerobic organism. Repeated cultures will give an index of progress in the fight to prevent a fatal termination. This procedure is not a difficult one to perform and it should be done more often than is customary.

Potassium permanganate has been used as an intrauterine douche in combating the anaerobic streptococci, and some authors have suggested that this method be used in treating the *B. welchii* infections within the uterus, although they fear air embolism. Is it not logical to assume that, as regards air embolism, it has been preceded by the gas resulting from the infection? The senior author decided that hydrogen peroxide and 10 per cent mereurochrome would cause a gentle debridement of the necrotic materials; the liberated oxygen would destroy the anaerobes; and the mereurochrome would destroy those organisms causing the mixed infection found in the more severe cases. He suggests that these intrauterine douches be repeated at least every other day because of the spore-bearing characteristics of the *B. welchii*. Vaginal instillations with the same mixture seemed to be efficacious in the treatment of the vaginal necrosis and were given twice daily. Nine of these cases reported have been under his supervision and no operation was performed.

Incision into the peritoneal cavity for drainage has been reported with fair results. Also, a number of cases of extirpation have been reported, the results have not been particularly gratifying on the whole. We have had little experience with such procedures. Unfortunately, the routine lochial smear and intrauterine culture in criminal abortion and suspicious cases has been discontinued on our service since 1934, so that 5 fatalities have occurred since that time, with clinical findings of *B. welchii* infection. But, we are reporting the proved cases and are omitting the unknown.

TABLE II. SUMMARY

	TOTAL NO. CASES	NO. MATERNAL DEATHS	NO. FETAL DEATHS	PER CENT MORTALITY		PER CENT CORRECTED MORTALITY (LIVED)	
				MATERNAL	FETAL	MATERNAL	FETAL
Local infection	6	0	2 (1 twin)	0	28.5	100	71.5
Gas sepsis	7	4	5	66½	71.5	33½	17½
Physometra	4	4	3	100	75	100	50
Or, Emphysema							

CONCLUSIONS

1. There is no specific cure for all cases.
2. Prompt massive doses of a polyvalent serum for streptococci and *B. welchii* upon admission, if present in the smears.

	GAS SEPSIS				PHYSOMETRA AND EMPHYSEMA								
	CASE 9	CASE 10	CASE 11	CASE 12	CASE 13	CASE 14	CASE 15	CASE 16	CASE 17				
Race	Colored	Colored	Colored	White	Colored	Colored	Colored	Colored	Colored				
Age	36	16	32	22	22	17	38	23	32				
Para	10	2	0	1	1	0	8	0	4				
Gestation	40 wk.	40 wk.	36 wk.	4 wk.	40 wk.	35 wk.	40 wk.	40 wk.	40 wk.				
Membranes ruptured	17 hr.	5 hr.	72 hr.	22 hr.	22 hr.	Intact on adm.	Intact on adm.	48 hr.	7 hr.				
Total hr. labor	21 hr.	13¼ hr.	96 hr.	None	47¾ hr.	38 hr.	72 hr.	72 hr.	63¼ hr.				
Type delivery	Postsection	Breech extrac-tion	Evisceration	Criminal abor-tion	Spontaneous	Spontaneous	Not delivered	Post-section	Craniotomy				
Temperature	98°	98.4°-104°	99°-101°	97°	98°-101°	99°-106°	100°-102°	Moribund	98°-102° x6				
Pulse	120	120-130	130-170	84-146	80-130	50-170	94-120	No pulse	110-120				
Respirations	22	22-52	42-60	30-50	22-32	20-46	24-30	None	24-30				
Blood Pressure	89/40	120/70-50/30	Not reported	90/45-80/40	110/80	200/130-120/80	150/110	20/00	90/60				
Hospital days	1¾ hr.	3	3	6	60	29	2	1 hr.	12				
Gas bubbles	Yes	None on Adm.	No	No	No	No	No	Yes	No				
Cultures													
Laboratory findings													
Complications													
Autopsy													

\*B. welchii.



showed gross evidence of gas bacillus invasion. Cultures from various organs produced heavy growths of *B. welchii* and hemolytic streptococci.

Following delivery the patient was given a single prophylactic dose of polyvalent serum. Sulfanilamide was given in large doses for the first few days, and two transfusions were given during the first week post partum. The temperature reached high points of 101° to 102° F. during the first five days, then dropped to normal and remained there until her discharge on the fifteenth post-partum day.

DR. R. J. CROSSEN, St. Louis, Mo.—At the St. Louis Maternity Hospital we have been using for years 1 per cent neutral acriflavine in glycerin, and it has cut down the incidence of infection very materially. We had a patient recently who went twelve days with ruptured membranes and no temperature elevation. I feel that the afebrile course and absence of infection were in a large part due to the use of daily vaginal instillations of acriflavine in glycerin during this period.

DR. RUSSELL (closing).—Many cases of *B. welchii* infection are probably not diagnosed because the attending physician fails to request smears from the cervix and vagina, as well as anaerobic cultures. This belief is substantiated by the fact that the senior author diagnosed, during one year, the greater number of cases appearing in the series by the above means. The economic importance of this organism cannot be underestimated as is shown by the history of the young child mentioned in this paper.

## PREVENTION OF TUBERCULOSIS BEGINS BEFORE BIRTH\*

### TUBERCULIN TESTING DURING PREGNANCY AS A FERTILE FIELD FOR CASE FINDING AND PREVENTION

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UDO WILE<sup>1</sup> stated that early diagnosis of syphilis in pregnant women is good economics, as it makes possible the treatment of two patients for the cost of one. Eisele and Mason<sup>2</sup> found the incidence of unsuspected tuberculosis in the routine prenatal clinic to be 1.06 per cent as compared to 0.87 per cent of syphilis in the same group. These figures point toward the fact that it is even more important to diagnose early tuberculosis in pregnant women than to diagnose early syphilis. Furthermore, Kuss, Comby, Hamburger and Binswanger have reported that "From slightly more than 1 per cent to 6 per cent of all deaths in children from birth to three months are due to tuberculosis. From the third to sixth month some authors have reported as high as 27 per cent of deaths have been due to this disease. Indeed more deaths from tuberculosis occur in the first year than in any one year of the three score and ten."<sup>3</sup> Therefore, tuberculosis case finding, to be most economical and effective, should begin in the prenatal group. In this way maternal diagnosis is made before the birth of the child and infection of a new generation is prevented.

Since July, 1936, the obstetric history sheet of the Santa Clara County Hospital has had a space for the tuberculin test report and since that

\*Presented in part by C. L. Ianne at the National Tuberculosis Association in symposium discussion of paper on "Mass Tuberculin Testing and X-raying."

3. Repeated intrauterine cultures, douches, and transfusions, as soon as the organism has been identified by smears and cultures.
4. It is important to differentiate in all cases of fever, jaundice, cyanosis, and endometritis.
5. Combat acidosis, anemia, and low urinary output.
6. Debridement of necrotic areas over the body and the application of an oxygen-liberating solution as a wet dressing.
7. Prophylactic doses in those cases with positive smears, only.
8. Early extirpation upon recognition of uterine emphysema, as may be proved by a skiagram.
9. Gas producing bacteria should be of extreme importance to doctors in contact with rural patients because these are often found in the intestinal tract of herbivorous animals.
10. Its prevalence has been proved; it is not confined to warm climates; and the cause of death may be attributed to an unknown etiology.
11. Escaping gas from the genital tract is indicative of a severe infection and a fatal termination of the case usually occurs.
12. All instruments and materials should be fractionally sterilized before being used again because of the spore-bearing properties of the organism.
13. Strict isolation precautions are of great importance.

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915 MADISON AVENUE

#### DISCUSSION

DR. LEONARD A. LANG, MINNEAPOLIS, MINN.—A case of *B. welchii* infection came to our attention during the past year. The patient, a twenty-seven-year-old primigravida, had been admitted to the hospital for induction of labor by rupturing the membranes, the indication being post maturity. She failed to go into efficient labor, however, and at the end of the fourth day the patient was found to be fairly exhausted, with a pulse of 100, a temperature of 100° F., the cervix 3 cm. dilated, fairly thick and edematous. The fetal head was well above the spines, well flexed, and there was no evidence of cephalopelvic disproportion. The cervix reached full dilatation forty-eight hours later. By this time the temperature had gradually risen to 102° F., and pulse remained at a level of 120. The fetal heart tones had disappeared some twelve hours before full cervical dilatation was accomplished. During this latter period the uterus had increased in size to a well-rounded, very tender organ in which it was difficult to distinguish the relaxation between pains, and a fairly abundant foul discharge had developed.

A craniotomy was performed when the cervix reached full dilatation. During delivery, large amounts of gas under pressure and foul discharge emanated from the birth canal. The fetus was autopsied, and heart, lungs, and liver especially

infected and the morbidity in the particular age and sex group in which the highest percentage of deaths occurs (Fig. 1).

The following cases will illustrate the damage done by unknown tuberculosis in the pregnant woman.

CASE 1.—A young married Mexican girl, aged 17 years, because of contact with one brother who died of tuberculosis and to a younger brother with generalized pulmonary tuberculosis, was examined in December, 1932 (aged 14), and again in December, 1933. Tuberculin test and x-ray of chest were negative. On June 20, 1935 the patient entered the hospital in labor, although otherwise apparently well. Physical examination of chest was negative. No x-rays of chest were taken. The child was born four days later and patient discharged after the usual time apparently well. Nine months later she attended the general medical clinic complaining of cough. A prescription was given for this and an x-ray taken with advice to return the following week. The cough subsided and the patient failed to return. She was seen by the tuberculosis clinic nurse a few months later during a visit to her brother

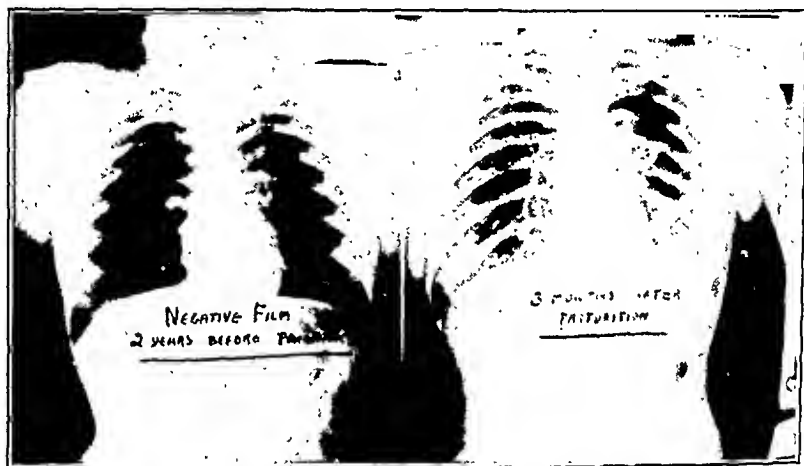


Fig. 2.—AL. Film Dec. 4, 1932: Chest clear. Film June 8, 1936: Shows mottling right upper half and infiltration left perihilar region.

in the sanatorium. Her general condition was noted and examination made. The film taken at this time showed progression of disease when compared with film taken on her first post-partum visit. Sputum was positive and patient admitted to the sanatorium June 16, 1936. Although apparently improving slightly at first, patient died in two years despite left phrenic paralysis, pneumothorax and pneumoperitoneum (see Fig. 2). She had nursed her child for ten months and, although chubby and apparently well, it was found to have bilateral bronchopneumonic pulmonary tuberculosis and died in the sanatorium, aged 18 months.

CASE 2.—A young American white woman, aged 20, contact with mother and a sister, both of whom died of tuberculosis, and whose younger sister later developed this disease, had a pregnancy with miscarriage, December, 1934. She became pregnant again and attended the prenatal clinic. No comments were found in case history indicating chest disease. Patient worked up to the date of delivery. She remained in bed one week after discharge and, suspecting her condition, weaned the child and went to see a private physician who referred her to the general clinic with a history that two days after the child was born, she began to cough and had about 5 c.c. of sputum. Night sweats, marked fatigue, and hemoptysis followed. On x-ray examination February, 1936, patient was found to have an advanced upper right lobe tuberculosis. She was referred to the chest clinic two weeks later and stated that previous to and during pregnancy she had "felt fine." No cough, fatigue, or

time, this test has been done routinely on each patient visiting the prenatal clinic. On those entering the hospital during labor, who have not attended the prenatal clinic, the test is done immediately after parturition. Those reacting are given a chest x-ray and if found to have pathologic shadows, are referred to the sanatorium for advice and care. While in the Obstetrical Division, these patients are isolated to prevent infection of the patient and hospital personnel.

A series of maternal and infant deaths from tuberculosis in 1934 and 1935 and the fact that several young mothers were found to have far advanced tuberculosis post partum, prompted us to perform tuberculin tests on the prenatal group. Two other factors helped to make our

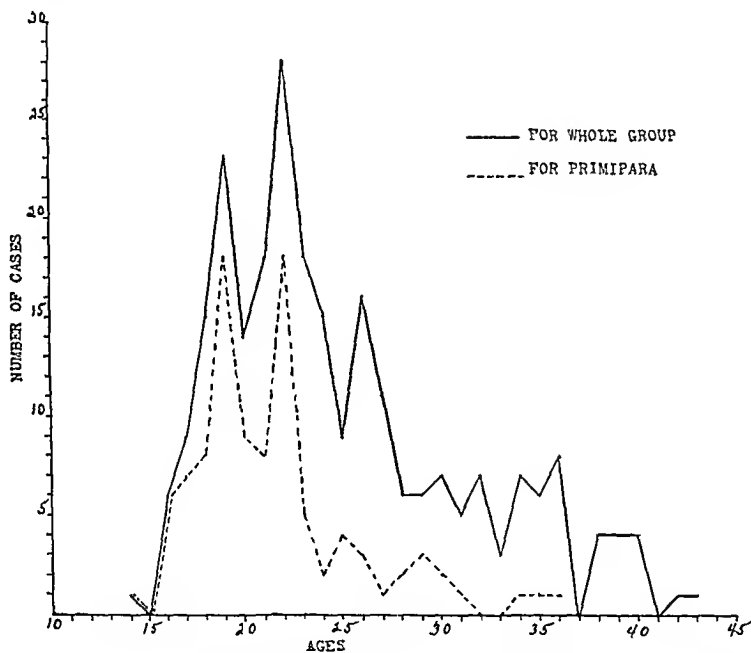


Fig. 1.—Graph showing age distributions of the 252 tuberculin reacting women and of the 97 primiparas who are included in the group.

obstetric service tuberculosis conscious: (1) the sanatorium division is adjacent to the general hospital and the interns and residents rotate part time through this service under supervision of the tuberculosis resident staff; (2) a member of the obstetric consulting staff had one year residency in the tuberculosis division.

The above cases were presented to the hospital staff meeting with the suggestion that all prenatals be tuberculin tested and the reactors x-rayed. This was finally approved but not without the usual fallacious comment: "Why tuberculin test when all adults are infected?"

Following the report of Korn<sup>4</sup> in the Cattaraugus County, N. Y., Milbank Survey that only about 50 per cent of adults in rural communities reacted to the tuberculin test, we began to test all adults attending the chest clinic and found many nonreactors. Testing prenatal women gives us a group tuberculin survey of supposedly normal young adults who are not tuberculosis suspects. It also gives a good idea of the number

At the end of the first six months of our survey, the figures were so impressive that a search of the literature was made, with the help of Dr. Kendall Emerson of the National Tuberculosis Association. This revealed that tuberculin testing has not been followed routinely in obstetric clinics. According to the Bureau of Maternal Welfare in Washington, nothing bearing on this work is on file in the United States Library. Vaughn<sup>5</sup> of Detroit states: "The tuberculin testing of prenatals is not a routine practice in our clinic. We are paying attention to individuals intimately exposed and those who live in areas of high mortality."

Through recent personal communication we find that Dr. Charles Cawood,<sup>8</sup> Health Officer of Fayette County, Kentucky, has also been tuberculin testing all patients attending the prenatal clinic since 1936.

Nicklas<sup>6</sup> mentions the use of the x-ray in finding early unsymptomatic tuberculosis in the expectant mother.

Although Block<sup>7</sup> of the University of Chicago considers the x-ray ideal for group examination, he feels that the expense makes it impractical and only x-rays those who have suspicious findings on fluoroscopic examination. He states the objections to this method of screening are the necessity for trained examiners and the element of time. In addition to the above, our objection is that the fluoroscope gives us no permanent record, and it does not reveal the total number of infected cases. Tuberculin testing tells us this and permits following of the family group. Block does not use the tuberculin test in group examination because of the large percentage who would fail to return for readings. We have overcome this difficulty by having the Public Health Nurse call and read the tests for those who fail to return. Block states that an additional objection to the tuberculin test as a method of screening out tuberculosis in adults is the high incidence of infection. He feels that it would be more economical to use the fluoroscope and x-ray only, whereas the test might be used successfully for children where the percentage of infection is much lower. This is not the case in our community where the percentage of infection in adults is 41 per cent, which is only a small percentage higher than in the high school group of a few years ago. We find that screening out negative reactors results in a definite saving of films and the time and work incidental to this procedure.

Other than the above references to early diagnosis, a review of the literature on tuberculosis and pregnancy disclosed mainly a discussion of the mortality and morbidity of tuberculosis during pregnancy. Most of this is very controversial and, except for personal impression and discussion as to whether pregnancy is harmful and whether it should be allowed to proceed or not, little is found.

Ornstein and others,<sup>9</sup> from a statistical study of a large group with tuberculosis, feel that pregnancy has little or no effect on the productive type of tuberculosis, whereas it is fatal to the exudative type. Skillen and Bogen,<sup>10</sup> in a study of 10,000 admissions to Olive View Sanatorium, Olive View, California, find that pregnancy in tuberculous women did not alter the fate of tuberculosis in comparison to a similar

other symptoms, except a loss of weight, were noted during pregnancy. Sanatorium care was advised for collapse therapy. She refused, feeling that she could take care of herself at home on bed rest, as had been advised several years before for a sister. Becoming worse on this regimen, she was admitted three months later with progressive disease and bilateral cavitation. At present she is barely holding her own with an ineffectual pyopneumothorax right and a fairly good collapse left.

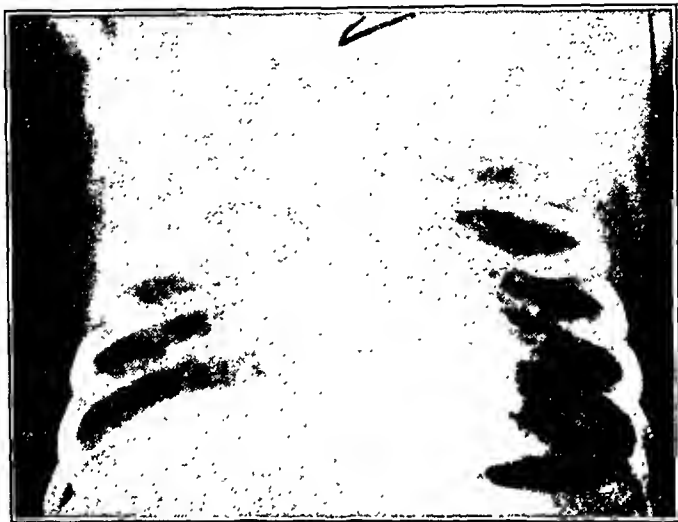


Fig. 3.—Baby L. Film Oct. 17, 1937 at age of twelve months shows bilateral generalized mottling. Child died aged 18 months.



Fig. 4.

Fig. 5.

Fig. 4.—RB. Film February, 1936: Shows heavy infiltration right upper with cavitation under clavicle.

Fig. 5.—Film Aug. 11, 1938: Shows bilateral partial artificial pneumothorax with numerous adhesions holding cavity open and fluid level above diaphragm. Left, artificial pneumothorax with heavy infiltration at base.

The child was taken to a nursery at ten weeks of age but not before infection had occurred as proved by positive tuberculin test. X-rays of the child's chest are apparently negative. Perhaps the fact that the child was weaned at ten days, when the mother recognized her condition, prevented repeated, massive infection, as occurred in Case 1.

TABLE II. PATIENTS WITH DEFINITE PULMONARY LESION FOUND AMONG POSITIVE REACTING PRENATALS

PT.	CASE	AGE	GRAV.	LESION	SPUTUM	DATE ADMISS- ION TO SANA- TORIUM	DATE OF DELIVERY	TREATMENT INSTITUTED	DISCHARGE AND CONDITION	TUBERCULIN TESTING OF CHILDREN			
										NEWBORN	OTHER, LIVE	POS.	NEG.
DB	2481	22	i	RL cavity with question- able infiltration. Second anterior I.S. upward. LL negative minimal tubercu- losis	None	2/27/37	5/17/37	Sanatorium care with Pnx. right Mar. 9, 1937. Baby cesarean section. Right Pnl. Jan. 19, 1938	Discharged July 29, 1937. Satisfactory Pnx. Syphilis under treatment	0	1	0	0
TO	2750	21	ii	RL soft infiltration 5th R.P. LL mottled density second anterior I.S. to apex. Moderately ad- vanced tuberculosis	None	6/17/38	6/10/38	Sanatorium care with phrenic crush, left. Pnx. failure July 11 and 19, 1938	Still in sanatorium	D at 2 mo.	0	0	1
MD	2473	27	iv	Far advanced bilateral tu- berculosis cavity	None	3/ 3/37	2/ 9/37	Sanatorium care. Prema- ture rupture of mem- branes. Dilatation and curettage. No Pnx. Pa- tient left	Patient signed a re- lease Mar. 28, 1937	Not tested	0	0	1
LG	252	34	xiii	RL minimal apical tuber- culosis	None	3/14/37	6/ 1/37	Sanatorium care with Pnx. right attempted. No space. Right phrenic crush Apr. 8, 1938. Pregnancy term. Feb. 15, 1938 at 4 mo.	Discharged Apr. 22, 1938. Satisfactory. At home	0	1	1†	9

Pnx, pneumothorax; Pnl, pneumonolysis; D, died; Stom, stomach; RL, right lobe; LL, left lobe; IS, interspace; RP, rib posterior.  
 †Child by first husband who had active far advanced tuberculousis.

nonpregnant group of women with tuberculosis, but that "The occurrence of pregnancy should not allow neglect of the pulmonary condition before, during and after obstetric management."

Before we began to discover early tuberculosis by tuberculin tests and before the general use of collapse therapy, it was our opinion that tuberculosis was definitely incited or made worse by pregnancy. Since the beginning of this survey we rarely find far-advanced tuberculosis in a post-partum patient.

Only three patients with far-advanced tuberculosis have been seen. One of them did not attend the prenatal clinic but was admitted in labor. This was during the early months of our survey and she was not tuberculin tested. One did not react to the first dilution of the test and delivered before the second dilution could be given. She was not x-rayed. This patient was admitted to the hospital twelve months post partum with hemoptysis and bilateral cavitation. The third had a positive tuberculin test but, due to clerical omission, this was not recorded on her chart and therefore no x-ray was taken. She was recently admitted to the sanatorium with far-advanced caseous cavernous tuberculosis.

This brings us to the conclusion that tuberculosis and pregnancy are not incompatible *if tuberculosis is diagnosed early and collapse therapy can be instituted.*

#### STATISTICAL STUDY

A total of 805 women were tuberculin tested; 114 women, or 14 per cent, failed to return for a reading. Of the 691 women who were tuberculin tested and read, 407, or 58.9 per cent, were negative and 284, or 41.1 per cent, were positive to a 1:1,000 dilution of old tuberculin. Of the 284 tuberculin reactors 252 were x-rayed. Thirty-two tuberculin reactors failed to return for x-rays. This may be attributed to the fear of some newlyweds to let their husbands know that they may have tuberculosis, as was suggested by Block in his Chicago survey.

Table I reveals the number of tuberculin reacting patients for each gravida and the mean age for each group. It is to be noted that 177 women, or 70 per cent, of the total 252 tuberculin reacting women x-rayed, were having their first, second, or third pregnancy. The average age of these 177 women comes well within the age group commonly reported as having the highest incidence of tuberculosis deaths (see Table I).

TABLE I. TWO HUNDRED FIFTY-TWO TUBERCULIN REACTING PREGNANT WOMEN

GRAVIDA	NO. PRENATALS	MEAN AGE
i	97	21
ii	47	23
iii	33	22
iv	18	26
v	14	24
vi	10	31
vii	6	33
viii	6	32
ix	3	31
x	5	32
xi	8	36
xii	2	33
xiii	2	35
xiv	1	40



## X-RAY FINDINGS

Of those x-rayed, 203 were found to have negative films; 37 had calcifications in the hilum or lung fields. Most of the latter were x-rayed or fluoroscoped three months after birth of child and none found to have activated. Twelve, or 1.7 per cent, had adult or reinfection type of lesion, mainly apical. Of these, 10 were minimal, 1 moderately advanced, and 1 far advanced. None had positive sputum. One was an observation case with infiltration of the left base, etiology undetermined. Upon pregnancy there was an extension of infiltration with positive stomach lavage and a diagnosis of minimal tuberculosis was established. The one with moderately advanced lesion was known to the chest clinic as an apparently arrested case; reactivation was suspected on pregnancy. The far-advanced case was definitely asymptomatic and not known to the clinic. In 5, diagnosis was established before the third month of pregnancy and 5 others one month or less before term. Two patients were found after delivery.

## TREATMENT

Sanatorium care was recommended for nine of these. Two (DB, MG) had pneumothorax established before term; 5 (LL, M.G., AT, JR, LR) as soon as they had convalesced from childbirth; 2 had temporary phrenic paralysis because of failure to induce pneumothorax. Only one of the above (LG) had hysterotomy with ligation of tubes. This was her thirteenth pregnancy and she had an active lesion. MD, with advanced tuberculosis, signed a release and left the sanatorium before pneumothorax was established. No follow-up was possible as patient had left the county. Two (IK, GV) had apparently arrested minimal lesions and modified bed rest was advised. One (RR) had no recommendation due to oversight (see Table II).

## FATE OF THE NEWBORN

A survey of the babies shows that 13 were born alive. One (LR) mother had a second pregnancy during the period of this survey. Eleven of the babies are still living. One died of injuries at four months; two of diarrhea at one and two months. Of the 11 living babies, 9 have been tuberculin tested, one reacting. The mother of this child had a minimal lesion which was overlooked but found on review of films after child was born. We have so far attempted to tuberculin test only the babies and other members of families where a reinfection type of lesion has been found.

## BENEFITS DERIVED

As mentioned above, we believe that prevention or postponement of actual disease by institutional care of the mother and initiation of collapse therapy before or soon after delivery is of great benefit. The family is spared a mother who would otherwise be an invalid. The newborn, the family, and the community are protected from the infection that occurs before symptomatic tuberculosis becomes manifest. Hospital patients are screened against a communicable disease and protection is afforded the hospital and patient personnel. Nursing the infant is prohibited and the massive infection that usually results in early infant death is prevented. The additional strain of caring for the child is obviated and the mother's general health is maintained. This period is considered by many to be the "last straw" in the causation of disease.

If the follow-up work is properly carried out, the remainder of the household is tuberculin tested and reactors x-rayed. *This is not done where the fluoroscope or x-ray is used as a screen.* Through this family follow-up, the husband of one of our prenatals, not in this group, was found to have a moderately advanced lesion with positive sputum and was removed to the sanatorium. In this case, infection of the newborn infant was definitely prevented.

MG 2555	31	vi	<i>RL</i> mottled density apex to fifth P.R. honeycombing. <i>LL</i> negative. Minimal tuberculosis right, fibroid	None	6/21/37	6/11/37	Sanatorium care. Pnx. right June 7, 1937	Discharged July 22, 1937. Pnx. discontinued by patient. Uneducated. Not being followed up	0	1	2	3
IK 2581	34	vi	Minimal apical tuberculosis fibroid arrested	None	Not admitted	6/5/37	Rest regime post partum at home	Satisfactory. Referred to sanatorium clinic for follow-up	0	1	1	1
LL 2723	17	i	<i>RL</i> mottling with calcification upper. <i>LL</i> soft infiltration second I.S. May 12, 1938 anti-partum moderately advanced tuberculosis	None	6/22/38	6/12/38	Sanatorium care. June 30, 1938 post partum. Cavity $3\frac{1}{2} \times 3$ cm. left. Pnx. left July 25, 1938	Still in sanatorium. Pnx. Satisfactory collapse	0	1	0	0
LR 2371	18	ii	<i>RL</i> soft foc. 1st. I.S. <i>LL</i> thumb print sixth I.S. Minimal tuberculosis	None	9/16/36	8/24/36 and 5/27/38	Sanatorium care. Pnx. Sept. 27, 1936. Baby cesarean section	Discharged Mar. 15, 1937. 2nd. pregnancy May 27, 1938 normal delivery	First D at 3 mo. 2nd not tested		0	0
RR 2826	33	ii	Minimal arrested tuberculosis. $???$ Child positive tuberculin test.	None	Not admitted	4/27/37	Home rest	Satisfactory	1	0	0	1
JR 2599	26	vi	<i>RL</i> soft mottling first <i>LL</i> second anterior I.S. to apex soft mottling. Moderately advanced tuberculosis	Negative	7/16/37 and 8/24/38	6/23/37	Pnx. bilateral. Right Oct. 18, 1937. Left Sept. 13, 1937. Pnl. bilateral because of adhesions	Still in Sanatorium	D at 3 mo.	3	5	0
AT 2374	19	ii	Suspicious tuberculosis May 20, 1933. Definite progressive with pregnancy. Minimal tuberculosis left	Neg. Stom. lavage pos.	4/1/38	11/10/36	Sanatorium care with Pnx. left. May 9, 1938	Pnx. O.K.	0	1	0	1
GV 2531	27	v	Minimal arrested tuberculosis right	None	Not admitted	12/16/37	Rest program at home	X-ray post partum O.K.	Not tested		0	2

## TREATMENT OF THE MENOPAUSE WITH ESTRADIOL DIPROPIONATE\*

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**A**N ESTROGENIC substance is any substance which has activities similar to those exhibited by the hormone of the ovarian follicle. In the human being, 3 chemically distinct and biologically active estrogenic substances have thus far been isolated. Estradiol has been separated from follicular fluid in crystalline form and presumably is the true follicular hormone.<sup>1</sup> Estrone (theelin) and estriol (theelol) are found in pregnancy urine,<sup>2</sup> placenta<sup>3</sup> and presumably in nonpregnant urine. They probably represent excretion forms of the metabolized estradiol.<sup>4-6</sup> Various observers do not agree as to the exact potency of these 3 compounds, but do agree that estradiol is more potent than estrone and that estriol is the least potent of the 3 substances.

It has been demonstrated by various workers that esterification of estradiol or estrone leads to a more prolonged physiologic effect on parenteral administration. This enhanced effect is due, presumably, to slower absorption of the compound.

In 1937 Miescher and Scholz<sup>7</sup> synthesized estradiol dipropionate, which is the doubly esterified form of estradiol. In this compound the 2 hydroxyl groups on the molecule have been replaced by propionic acid radicles. Miescher, Tschopp and Scholz<sup>8</sup> have investigated the relative potency of this substance, with other esterified forms and with free estrone and estradiol. According to these workers the minimal effective dose or rat unit of estrone, estradiol benzoate, and estradiol dipropionate is the same, 0.00075 mg. Other workers agree fairly well on this rat unit for estrone but believe the rat unit for estradiol benzoate to be lower. Miescher and his co-workers found a marked difference in physiologic effect between these compounds. If 0.05 mg. of estrone, estradiol benzoate, or estradiol dipropionate were injected into castrate rats, the animals would go into estrus. In the estrone injected animals this estrus would persist for four or five days. In the animals injected with estradiol benzoate, estrus would persist for fourteen days. In animals injected with estradiol dipropionate, estrus would persist for forty-two days. Similar differences were noted when growth of the rat uterus was used as the criterion of estrogenic effectiveness. With the same dosage (0.05 mg.) the effect of estrone persisted eight days, with estradiol benzoate twenty-four days, and with estradiol dipropionate, sixty days.

The value of estrogenic substances in the treatment of menopausal symptoms is quite well established. However there is little agreement of opinion as to which substance should be used, or the method or frequency of administration. We are well aware of the fact that desiccated thyroid or sedatives may be of value in some menopausal patients. Some individuals may even be improved by suggestion therapy. However, it

\*Presented at a meeting of the Chicago Gynecological Society, March 17, 1939.

# SUMMARY

After some seemingly unnecessary tuberculosis deaths following pregnancy, tuberculin tests, with x-rays of the reactors, were added to our routine procedure for the examination of prenatales.

Between June 1, 1936, and June 1, 1938, 805 women in the so-called "dangerous" age were tested. Six hundred ninety-one tests were read. Two hundred eighty-four, or 41+ per cent, reacted and 407, or 58.9 per cent, did not react to old tuberculin 1:1000. Of the reactors 252 were x-rayed; 32 failed to return. The x-rays revealed 10 cases of minimal tuberculosis, one moderately advanced, and one far advanced. Nine were admitted to the sanatorium before or immediately after delivery and pneumothorax established in seven. Two had phrenic paralysis when pleural space was not found. Three with inactive lesions were treated at home.

None of the reactors, including those with lesions, have had extension or clinical manifestation of disease. Most of the mothers with satisfactorily established pneumothoraces are home earing for their families. Only one of the children has been infected to date. It is gratifying to note that there have been only two deaths in the first year of life since 1934 in Santa Clara County, a mixed urban and rural community of 160,000. These occurred in 1935. In 1937 there was only one death in the age group from one to ten years.

# CONCLUSIONS

1. The routine use of the tuberculin test in prenatal care is a method that can be easily used in clinics and private practice for discovery of active tuberculosis.

2. Forty-one per cent of patients who returned for reading had positive tuberculin tests.

3. Unsuspected, active tuberculosis occurred in 1.7 of those read.

4. The cost of fluoroscopy or x-ray for the tuberculin reactors would be very little more than the cost of routine Wassermann.

5. Early diagnosis permits early institution of collapse therapy, thus permitting pregnancy to continue without extension of pulmonary disease.

6. Although this is a small group and the time elapsed short, the findings are of sufficient public health value to recommend it as a routine preventive measure. Prevention of tuberculosis should begin before birth.

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The dispensary patients were seen once a week, the few private patients occasionally at more frequent intervals. It was found that patients were rendered symptom-free more rapidly by giving large doses (2.0 to 5.0 mg.) for the first few treatments. No patient was treated more often than once a week. After a patient was free from the hot flushes (usually one to three weeks) an attempt was made to determine her maintenance dosage. This was a rather difficult procedure, being largely a matter of trial and error. However, by gradually lowering the dose, and prolonging the interval between treatments, at least the approximate maintenance dosage was determined which would keep each patient either entirely symptom-free or having not more than 1 or 2 hot flushes during the course of a week.

A slight diminution in necessary dosage was observed in only a few patients during the experimental period. This is probably due to the fact that only a relatively short period of treatment is considered in this study. Patients included in this series are limited to those treated from three to nine months only.

Slight and temporary reappearance of symptoms was noted in a few patients, associated with upper respiratory infections, or periods of unusual emotional stress.

The ages of the patients in this series varied from 29 to 59 years, with an average age of forty-three years. Twenty-nine were "normal" menopausal patients, 23 postoperative and 3 postradiation. The average age of the patients and the average duration of the symptoms are shown in Table I. There was no definite correlation between the necessary maintenance dosage and either of these factors. The total dosage per month per patient has also been calculated but no definite correlation was found with the age or length of symptoms.

In theory, at least, one would expect that the necessary maintenance dosage would be less in patients whose symptoms had been present a long time in contrast to those in whom the symptoms were of recent origin. In a larger series of patients such a correlation might be present.

TABLE I. DETAILS OF TREATMENT

DOSE IN MG.	INTERVAL IN WEEKS	NUMBER OF PATIENTS	AVERAGE LENGTH OF SYMPTOMS MONTHS	AVERAGE AGE YEARS
0.2	2	1	6.0	36.0
0.5	1	3	6.0	49.7
1.0	1	6	7.8	41.0
1.0	2	14	12.3	42.3
1.0	3	2	6.5	42.5
1.0	4	1	12.0	48.0
2.0	1	6	37.0	45.0
2.0	2	3	14.25	37.3
5.0	1.0	6	10.0	42.0
5.0	1.71	3	19.5	43.6
5.0	2.0	7	38.0	43.0
5.0	3.0	2	30.0	40.5
5.0	4.0	1	12.0	59.0

TABLE II. NECESSARY FREQUENCY OF TREATMENT

	TREATED ONCE A WEEK	TREATED EVERY 10 DAYS	TREATED EVERY 2 WEEKS	TREATED EVERY 3-4 WEEKS	TOTALS
Number of patients	21	3	25	6	55
Per cent of patients	38.18	5.45	45.45	10.92	100
	TREATED EVERY 7 TO 10 DAYS	TREATED EVERY 2 TO 4 WEEKS	TOTALS		
Number of patients	24	31	55		
Per cent of patients	43.64	56.36	100		

is very doubtful whether true menopausal symptoms such as the hot flush can be relieved in all patients by such means. Estrogens, if given in adequate dosage, will relieve these symptoms in all patients. The one qualification that must be added to this statement is that the symptoms the estrogens are expected to relieve must truly be menopausal symptoms and not entirely independent or even unrelated symptoms present in the woman of menopausal age.

Estrogens are effective by a variety of routes: the oral, the percutaneous or the parenteral. With the exception of estriol glucuronide (emmenin)<sup>9</sup> which is of low potency, natural estrogens are many times more effective by parenteral administration than when given orally. Estrogens are at the present time quite costly. Their price per effective mouth unit is such that treatment of the ordinary patient with dosages adequate to control menopausal symptoms is financially prohibitive.

Several workers have shown that estrogens are absorbed through the skin and have systemic effects after percutaneous administration.<sup>10-13</sup> According to Zondek<sup>10</sup> estrone in solution in alcohol, benzene, or ether is as effective percutaneously in the experimental animal as it is subcutaneously in oil. In oil or ointment solution it is only one-seventh as potent percutaneously as it is subcutaneously. Whether this relative effectiveness by percutaneous administration is equally as true in the human being has yet to be shown. A report by Salmon<sup>13</sup> and experiments in progress by one of us (R. R. G.) would indicate that this is doubtful.

At the present time the majority of patients are given estrogenic therapy by the intramuscular route. In this country, at least, injections are usually given 2 to 4 times weekly. Intramuscular injections are not pleasurable. Any estrogenic substance, then, that would control menopausal symptoms and that which could be given with a minimal frequency would be desirable.

In view of the enhanced potency and prolonged physiologic effect of estradiol dipropionate in the experimental animal, it was thought worth while to determine the clinical value of this substance in the treatment of menopausal symptoms in the human female.

#### METHODS AND RESULTS

Sixty-two menopausal patients have been treated with estradiol dipropionate.\* Only 55 of these patients will be considered in this report. The remaining 7 patients are not included either because they had been observed over too short a period of time (under three months) or because their clinic attendance was so poor that it was not possible to estimate their maintenance dosage.

The symptoms of the menopausal patient are many and varied. However, such patients have one common symptom, the hot flush. In view of this fact, the patients were instructed to keep an accurate record of the frequency and severity of the hot flushes. These data were used to a large extent as the index of the success of therapy. It was noted that with disappearance or return of the hot flushes there was a corresponding subsidence or exacerbation of such symptoms as nervousness, irritability, fatigue, headaches, etc.

\*Estradiol dipropionate under the trade name "Di-ovocyclin" has been furnished through the courtesy of Dr. Ernst Oppenheimer of Ciba Pharmaceutical Products Incorporated.

Two of these patients received 1.0 mg. once every two weeks and their smears were consistently of the menopausal type under treatment with both estradiol dipropionate and estrone. In the other 4 patients with dosages of 1.0 or 2.0 mg. of estradiol dipropionate per week the smears were of the estrus or follicular type. When estrone was substituted after a lag of one or two weeks the smears regressed toward the menopausal types containing varying proportions of squamous epithelial cells, small round epithelial cells and leucocytes. One to two weeks after estradiol dipropionate was resumed, the smears again returned to the estrus type.

In addition to these menopausal patients, vaginal smears were made weekly on 4 patients who had been treated and cured of a vaginitis with estradiol dipropionate. One patient with senile vaginitis had been found to maintain a consistent smear of squamous epithelial cells on 1.0 mg. of estradiol dipropionate once a week. When estrone was substituted, there was a gradual regression of the smear to the menopausal type. At the end of the third week of estrone the smear consisted of equal proportions of squamous epithelial cells, small round epithelial cells and leucocytes.

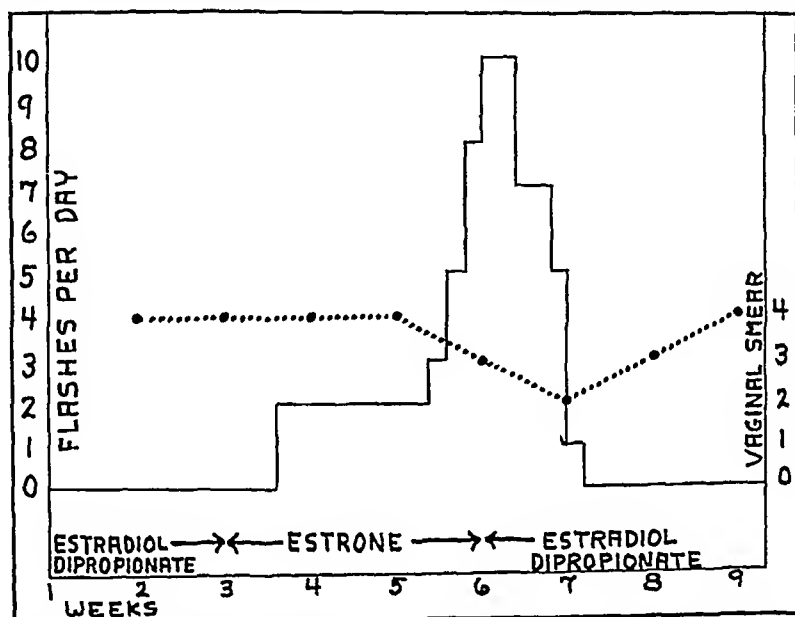


Fig. 1.—Solid line shows number of hot flashes per day. Dotted line shows state of vaginal smear. This patient had been standardized at 2 mg. of estradiol dipropionate for six months. 4, Smear of squamous epithelial cells. 3, Smear of squamous epithelial cells and small round epithelial cells. 2, Smear of few squamous, many small round epithelial cells and a few leucocytes. 1, Smear of small round epithelial cells and leucocytes in equal proportions. 0, Smear of mostly leucocytes and a few small round epithelial cells.

Three other patients had been treated for infantile vaginitis. In these patients it had been found that an estrus smear could be maintained for two weeks with 1.0 mg. of estradiol dipropionate. When estrone was substituted and the smear examined one week later, in addition to squamous epithelial cells, a few small round epithelial cells and leucocytes were found in 2 of these patients. At the end of the second week the smears in both had regressed almost completely to the infantile type. In the third patient, it was found that estrone would maintain the estrus smear for one week, but at the end of the second week the smear was made up of small round cells and leucocytes.

On the basis, then, of recurrence of subjective symptoms in 10 of 11 menopausal patients and objective vaginal smear changes in 8 patients, estradiol dipropionate is clinically more effective per milligram in the human being than is estrone.

#### DISCUSSION

This clinical study must not be interpreted as presenting data as to the absolute minimal, total dosages of estradiol dipropionate necessary to

The necessary frequency of treatment is shown in Table II. Twenty-one of the 55 patients had to be treated once a week for maintenance therapy, 3 every ten days, 25 every second week, and the remaining 6 every third or fourth week. A further analysis of these data shows that 43.64 per cent of the patients could be maintained with treatment once every seven or ten days and 56.36 per cent of the patients by treatment once every second to fourth week.

These data indicate that estradiol dipropionate is clinically valuable in that treatment may be given at relatively infrequent intervals. The individual dosages may seem quite high but the dosage when considered on a monthly basis is not very large in the majority of patients (Table III). The maintenance dosage per four weeks in the 55 patients was 2.0 mg. or less in 21, 4.0 to 5.0 mg. in 10, 7.5 to 10.0 mg. in 15 and 15.0 to 20.0 mg. in 9; 56.36 per cent of the patients received 5.0 mg. or less per month and 27.27 per cent received 7.5 to 10.0 mg. per month; 16.37 per cent received what may be considered a fairly high dosage of 15.0 to 20 mg. per month.

TABLE III. TOTAL DOSAGE PER 4 WEEKS

	2.0 MG. OR LESS	4.0 TO 5.0 MG.	7.5 TO 10.0 MG.	15.0 TO 20.0 MG.	TOTALS
Number of patients	21	10	15	9	55
Per cent of patients	38.18	18.18	27.27	16.37	100
	5.0 MG. OR LESS		7.5 TO 20.0 MG.		TOTALS
Number of patients	31		24		55
Per cent of patients	56.36		43.64		100

Patients were observed and questioned for systemic reactions but none were noted. Twelve patients had some recurrence or exaggeration of uterine bleeding. In 3 patients the bleeding was rather profuse but ceased when treatment was discontinued for a short interval or when the dosage was lowered.

A comparison of the clinical effectiveness of identical amounts of estradiol dipropionate and estrone has been made. Eleven patients of this series whose maintenance dosage of estradiol dipropionate had been determined, have been given the same amount in milligrams of estrone at the same time intervals. The patients were not informed of this substitution. Ten of the 11 patients had a recurrence of symptoms under treatment with estrone. When estradiol dipropionate was again given, the symptoms disappeared.

One patient of this group (Fig. 1) had a maintenance dosage of 2.0 mg. of estradiol dipropionate once a week. When estrone was substituted symptoms recurred in five days. Six patients had a maintenance dosage of 1.0 mg. of estradiol dipropionate once a week. When estrone was substituted symptoms recurred in 5 of 6 patients in one to two weeks (average 1.6 weeks). Findings in the sixth patient are considered inconclusive because of irregular attendance to the clinic. Three patients had a maintenance dosage of 1 mg. of estradiol dipropionate every two weeks. With estrone symptoms recurred after two to four weeks (average 2.66) of treatment. One patient had previously been treated with 0.2 mg. of estrone a week with some improvement but not complete cessation of hot flushes. Her maintenance dosage of estradiol dipropionate for complete relief of symptoms was found to be 0.2 mg. of estradiol dipropionate every two weeks. When estrone was substituted flushes recurred at the end of the third week. One week after the return to estradiol dipropionate, symptoms ceased.

Weekly vaginal smears have been examined on 6 of these menopausal patients. The smears have been interpreted according to the criteria of Papanicolaou (Fig. 1). He has shown that in the human being the menopausal smear is characterized by few or no squamous epithelial cells and with varying proportions of small round epithelial cells with large nuclei and leucocytes. Under adequate estrogenic therapy the vaginal smear consists almost exclusively of large flattened squamous epithelial cells with small darkly staining, pyknotic nuclei.



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## DISCUSSION

DR. M. EDWARD DAVIS.—This report on the treatment of the menopause with estradiol dipropionate emphasizes the importance of choosing the proper available estrogenic substance. The prolonged and more pronounced effect of this estrogenic hormone which probably represents the true follicular substance simplifies therapy and provides more favorable results. Our work confirms all of the observations of the authors.

Some time ago we began the use of estrogens in suitable ointments for local application. This method of therapy should theoretically be ideal for it obviates the necessity of hypodermic administration and provides a constant hormonal effect. We have used this preparation in approximately 40 patients with menopausal symptoms and have found that it was of value in less than half of this group of women. In a number of our patients this type of medication provided only partial relief. From these preliminary observations, we have concluded that estrogens cannot be provided the patient as readily by the percutaneous route as by hypodermic administration.

Dodds, Lawson, and their co-workers have more recently introduced synthetic compounds with estrogenic activity. During the last year these compounds have been available for animal experimentation and clinical use. Most of these synthetic organic compounds are derived from a chemical compound designated as stilboestrol by Dodds and others. It has been found that these substances are several times more active than the natural estrogens, that they produce all of the changes that can be ascribed to the use of natural substances, and that they are as effective by oral administration as when administered parenterally. These substances provide us with a new type of medication, for oral administration is most desirable. These synthetic compounds will likewise reduce tremendously the cost of estrogenic medication. During the past four months we have treated a number of patients with these artificial estrogens and have secured excellent results. The only undesirable manifestations which we have noted have been occasional nausea, vomiting, and headache. Only additional observations will determine whether these manifestations occur too often to make the use of these preparations undesirable.

It is our impression that these new synthetic organic compounds will simplify the therapy of the menopause as well as the treatment of all other conditions where estrogens have been found effective.

DR. R. R. GREENE (closing).—By "natural estrogens," we meant the natural estrogens found only in the human being. There are several other estrogens found in animals, as for example in the pregnant mare.

We have had no experience with the stilboestrol referred to by Dr. Davis. The matter of nausea and vomiting with this particular substance is an observation not only on the part of Dr. Davis but also in the English literature, where there are 6 reports concerning patients who were given it by mouth. One man gave it by subcutaneous injection, and he also reported nausea and vomiting. The amount of nausea and vomiting varied from 9 per cent to 68 per cent of the patients in the different reports. Whether this nausea and vomiting is inherent in the stilboestrol or is due to too rapid absorption is not known. Recently it has been esterified and has been used in animals in the form of the dipropionate, where it also has a prolonged action. We hope when used in the human being in the esterified form that it will not have these undesirable features.

control symptoms in menopausal patients. The emphasis has rather been on an attempt to determine if this substance would be clinically valuable when given in moderate dosages at infrequent intervals. It is quite possible that some of the patients who received treatment of 1.0, 2.0, or 5.0 mg. at two- to four-week intervals could have been maintained with smaller, total monthly dosages if treated at more frequent intervals. At any rate, this particular substance has a prolonged effect in the human being similar to that observed in the rat.

This prolonged clinical effectiveness is qualitative. It is not due merely to the dosages used. This is indicated by the fact that estrone, a substance that is supposed to have the same minimal effective dose or rat unit has been subjectively and objectively inadequate when substituted for estradiol dipropionate.

We do not, however, wish to indicate that we consider this method the only way to treat patients with estrogenic substances or that estradiol dipropionate is the one and only ideal estrogenic hormone. It is possible that in the near future the natural estrogens (estrone, estradiol, estriol) will become sufficiently inexpensive for all such therapy to be given by mouth. This oral route would probably be preferred by many patients. It is also possible, though, that some would prefer an intramuscular injection once every one or four weeks rather than a pill by mouth 3 times each day.

Another possibility is that the use of the natural estrogens in the free or esterified forms will be completely supplanted by the new potent estrogens of a more simple chemical structure as discovered by Dodds and his co-workers.<sup>15-17</sup> One of these synthetics, di-ethyl stilboestrol, has been used for estrogenic therapy in human beings by several English workers.<sup>18-23</sup> These workers have reported, however, nausea with occasional vomiting and epigastric pain in 9 per cent to 67.7 per cent of treated patients. It remains to be seen whether this complication is merely due to the method of administration or is inherent in the compound.

#### SUMMARY AND CONCLUSIONS

Estradiol dipropionate has been shown by previous workers to have a very prolonged estrogenic effect in the experimental animal. Evidence is presented that this compound also has a prolonged effect in the human being. It is of unusual clinical value in that injections may be given at infrequent intervals. A comparison with estrone has shown estradiol dipropionate to be clinically more effective.

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for 4 years when pregnancy occurred (1935); a second pregnancy occurred in 1936 with delivery at term of a 10-pound child. Menses have continued periodically. Menstrual calendar records: 1938, 9 cycles, 28 to 37-day intervals. Last examination, December, 1938; no recurrence of cystic ovaries or amenorrhea; eight years postoperative.

CASE 3.—L. C., April, 1929; aged 21 years, married 2 years. *Amenorrhea, 1 to 9 months, usually 6 months; sterility.* Hormone therapy for past 4 years. X-ray therapy to ovaries, December, 1929—no apparent effect. Repeated hormone therapy with some improvement and pregnancy, October, 1931. After delivery, secondary amenorrhea occurred and lasted 21 months in spite of hormone therapy. Examination revealed enlarged and tender ovaries and a pneumoroentgenogram in July, 1933, corroborated the findings. October, 1933: bilateral wedge resection was done and regular menses followed monthly. Two pregnancies and full-term deliveries in 1935 and 1935. Calendar record of menses: 1936, 10 periods at intervals of 27 to 39 days; 1938, 5 periods, 28 to 31 days. Last examination, August, 1938; no recurrence of cystic ovaries; 5 years postoperative.

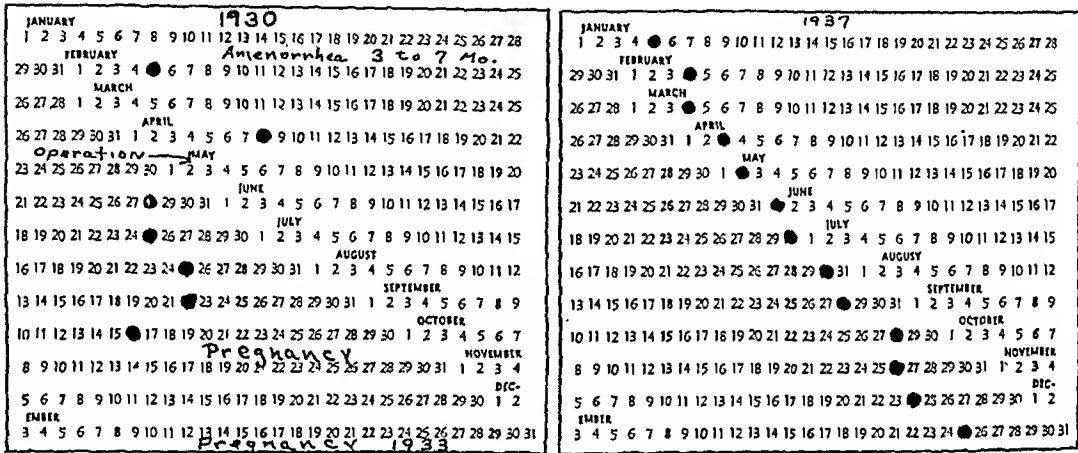


Fig. 1.—Case 1, M. G. Calendars of menstrual periods, showing establishment of regularity in 1937, after operation in 1930.

CASE 4.—H. W., January, 1933; aged 23 years, married 3 years. *Amenorrhea, 1 to 6 months, usually 3 or 4 months; sterility, 2 years.* Hormone therapy failed. On examination, the left ovary was found palpably enlarged and pneumoroentgenogram revealed that both ovaries were cystic. March, 1933: bilateral wedge resection. Regular menses for next 18 months; examination in March, 1934, revealed a normal pelvic status with no recurrence of cystic ovaries. In response to follow-up inquiry, it was learned that one pregnancy resulted.

CASE 5.—O. B., January, 1933; aged, 25 years, married 1½ years. *Irregular menses every 2 or 3 months; sterility.* Palpation revealed a cystic right ovary; pneumoroentgenogram showed both ovaries polycystic. Bilateral wedge resection performed, followed by regular monthly periods. Examination in September, 1934, and June, 1935, revealed no recurrence of the cystic ovaries. There was an additional male factor in the sterility picture; i.e., neerospermia. 1933: 11 cycles, 26 to 31-day intervals, usually 27; 1934: 11 cycles, 28 to 35 days, usually 29; 1935: 5 cycles to June, 26 to 31 days.

CASE 6.—E. A., October, 1933; aged 33 years, married 15 years. *Amenorrhea, 5 to 9 months with increasing intervals.* Both ovaries were palpably enlarged and cystic; these findings were verified by pneumoroentgenogram. Hirsutism and pain in the right lower quadrant were additional complaints. A bilateral wedge resection was performed and follow-up for eleven months revealed regular monthly periods and no recurrence of the cystic ovaries. No further follow-up response.

## SURGICAL TREATMENT OF BILATERAL POLYCYSTIC OVARIES—AMENORRHEA AND STERILITY\*

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DURING the past ten years, we have particularly interested ourselves in patients whose principal complaints were amenorrhea and sterility and in whom we found bilateral polycystic ovaries. Partial oophorectomy by wedge resection was performed upon such patients with satisfactory results. In a previous paper (Stein and Leventhal<sup>1</sup>) on this subject, we reported 7 cases. We now desire to record the subsequent course in 6 of the 7 patients whom we were able to follow, and to report 21 additional cases. Patients who complained primarily of bleeding rather than of amenorrhea were omitted from this series even when the ovaries were involved. In many of the patients herein reported, menstruation was normal for a variable time after puberty, when irregularity developed. In some women, this was accompanied by excessive menstrual bleeding followed by increasingly extended intervals. This eventuated in a true amenorrhea which in several instances lasted from two to eight years. In some, particularly in single girls observed during adolescence, menstruation had never been definitely established with only occasional spotting prior to the development of amenorrhea. These varied symptoms were evidence of disturbed pituitary-ovarian relationship, resulting finally in amenorrhea and/or sterility. In this latter stage, both ovaries were found enlarged and polycystic. The symptomatology as observed in these patients, as well as anatomic characteristics of the ovaries, were fully described in the previous article.

### PREVIOUSLY REPORTED SERIES

CASE 1.—M. G., first observed in October, 1928; aged 22 years; married 1½ years. *Irregular menses.* Hormone therapy failed. January, 1930, complained of sterility and 2 to 7 months' amenorrhea. Pneumoroentgenogram revealed bilateral polycystic ovaries. May, 1930, bilateral wedge resection. Result: regular menses until October, when pregnancy occurred, with delivery at term. Menses normal and regular until February, 1933, when second pregnancy occurred; full term delivery. During 1937, laparotomy for gall bladder disease disclosed normal ovaries; no adhesions. Menstrual calendar records: 1937, 12 cycles; intervals of 28 to 31 days; 1938, 12 periods, 27 to 33 days. Last examination, April, 1938: no recurrence of cystic ovaries or amenorrhea—nine years postoperative (Fig. 1).

CASE 2.—B. K., August, 1931, aged 29 years; married 5 years. *Eight-year amenorrhea; five-year sterility.* Hormone therapy for one year prior to admission with no benefit. Hirsutism marked. Pneumoroentgenogram revealed bilateral polycystic ovaries. Bilateral wedge resection was followed by regular monthly periods

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2 very scant periods from February, 1935 to October, 1936. Pneumoroentgenogram revealed a small uterus and bilateral polycystic ovaries. December 15, 1936: bilateral wedge resection performed, followed by irregular menses. Pregnancy six months later. Menses regular since; pelvic examination in February, 1938 revealed no evidence of recurrence of cystic ovaries. Second pregnancy, August, 1938. Pathology (No. 3222): Fibrosis of ovary; several large follicle cysts; thick tunica; luteinized theca interna.

CASE 12.—R. F., May, 1936, aged 28 years, single. *Complained of 2 months' amenorrhea*, and irregularity for past year. Marked hirsutism and obesity. Recto-abdominal findings indefinite. Complete metabolic work-up and x-ray of sella turcica were negative. Pneumoroentgenogram revealed bilateral cystic ovaries. Bilateral wedge resection performed in June, 1936. Uterus was small and both

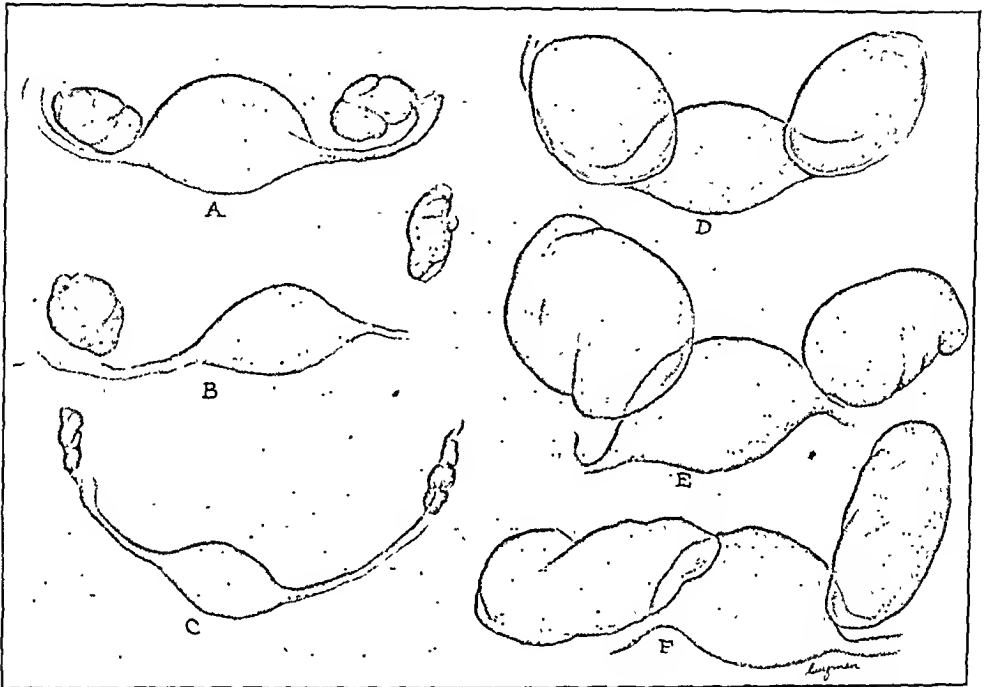


FIG. 2.—Comparative drawing illustrating the pneumoroentgenograms of A, Normal uterus and ovaries; B, uterine hypoplasia; C, fetal type uterine and ovarian hypoplasia; D, juvenile uterus, bilateral polycystic ovaries, Case 13; E, normal uterus, bilateral polycystic ovaries (large), Case 22; F, normal uterus, bilateral polycystic ovaries (oyster ovaries), Case 19.

ovaries polycystic. Following operation, menses were at intervals of 29 to 33 days, and in 1937, there were 11 periods, 31 to 40 days. Patient has left city. On written report, Jan. 1, 1938, patient is in good health and menstruating regularly. Pathology (No. 1530): multiple follicle cysts; atretic follicles; *Corpora albicantia*; luteinized theca interna.

CASE 13.—L. G., September, 1932, aged 14 years, single. *Menstruated every 3 months in past year*. Physical development masculine in type with marked hirsutism of face and body; breasts underdeveloped. Rectal palpation revealed a small uterus and indefinite adnexal findings. Pneumoroentgenogram in 1932 revealed a small uterus, and cystic ovaries. In June, 1933, she again complained of 2 to 3 months' amenorrhea and persistence of marked hirsutism. Second pneumoroentgenogram revealed cystic ovaries to be larger than on previous examination. Bilateral wedge resection, August, 1934. In 1936, periods were 21- to 27-day intervals, and in 1937, there were 12 periods of 19 to 28 days; in 1938, there were 11 periods at intervals of 25 to 34 days, but usually 27. Last examined in September, 1937: no recur-

CASE 7.—M. B., August, 1933; single, aged 20 years. *Amenorrhea, 2 to 4 months; pain in both lower quadrants.* Rectal examination revealed both ovaries enlarged and cystic; these findings were corroborated by pneumoroentgenogram. Bilateral wedge resection was performed. The pain was relieved and regular menses were restored. Marriage a few months later, followed by regular periods. Menstrual calendars revealed: 1934: 9 cycles, 29 to 35-day intervals; 1935: 11 cycles, 28 to 34 days. Pregnancy, 1936, with delivery at term. Calendar record for the year following showed cycles of 30 to 34-day intervals. Last examined in July, 1937, at which time no recurrence of the cystic ovaries was found—5 years postoperative.

The results in these cases answer the objections of some gynecologists that partial ovarian resection is temporary in effect and is likely to be followed by recurrence. No recurrence has been observed in this series of patients, 5 of whom were followed from five to nine years postoperative. Furthermore, the fact that 5 of the 7 patients had 8 pregnancies subsequent to operation is testimony of restored fertility. One was lost sight of, and one with regular menses presented a male sterility factor. These women are enjoying good health (Fig. 2).

#### ADDITIONAL CASES

CASE 8.—E. A., July, 1935; aged 24 years, married 3 years. *Menses irregular, 1 to 2½ months; sterility, 3 years.* Following irregular bleeding, a tender mass was found in the left adnexae which led to the diagnosis of tubal pregnancy. At operation, a ruptured corpus luteum cyst with free blood in the peritoneal cavity was found. In addition, both ovaries were found to be polycystic. Bilateral wedge resection was performed. The next seven periods were reported to be of 29-day intervals. Examination showed no recurrence of cystic ovaries. Menstrual calendar for 1938: 27- to 32-day intervals, usually 29 days. Pathology (No. 1722): Hemorrhagic corpus luteum cyst; multiple follicle cysts; primordial follicles.

CASE 9.—M. E., February, 1937; aged 25 years, single. *Always irregular periods, usually 4 to 8 weeks; painful and often profuse.* Both ovaries cystic and tender on rectal palpation. Hormone therapy failed to relieve. Pneumoroentgenogram showed a small uterus and bilateral cystic ovaries. Dilatation and curettage and bilateral wedge resection performed April, 1937. Endometrium was in proliferating phase. From August, 1937, to December, 1938, 17 periods monthly at intervals of 27 to 35 days. Last examined in August, 1937, at which time there was a normal pelvic status with no recurrence of cysts. Pathology (No. 1083): Numerous follicle cysts; Corpora albicantia; fibrosis of ovary; moderately thick tunica; luteinized theca interna; old corpus luteum; secretory endometrium.

CASE 10.—H. E., September, 1935; aged 22 years, single. *Complained of seven months' amenorrhea.* Severe facial acne, marked hirsutism—masculine type. Rectal examination revealed both ovaries somewhat enlarged. Pneumoroentgenogram showed a small uterus and bilateral cystic ovaries. Hormone therapy for several months with no benefit. Pneumoroentgenogram repeated. Operation, February, 1936: hypoplastic uterus, both ovaries adherent, right containing a small chocolate cyst; both ovaries polycystic. Bilateral wedge resection including cyst area. Immediate improvement in patient's general health and complexion but no return of regular menses until 1938, when she had monthly periods of 19- to 36-day intervals. However, 7 of the 12 periods varied only 2 days. Last examined in June, 1937, at which time there was no evidence of recurrence of cystic ovaries. Pathology (No. 562): Endometriosis; mature Graafian follicle adjacent to follicle cyst; very thick tunica (the mature Graafian follicle is considerably below the surface); large follicle cysts; marked luteinization of theca interna.

CASE 11.—L. F., February, 1935, aged 31 years, married 2 years. *Complained of 4 months' amenorrhea and of sterility.* Hormone therapy of no benefit. Only

right ovary enlarged and cystic; the left ovary was not visualized. At laparotomy both ovaries were typically polycystic. A bilateral wedge resection was performed. Postoperative examination in February, 1939, showed no recurrence. Had three menstrual periods since operation (4 months previously). Pathology (No. 3000): Fibrosis of ovary; *Corpora albicantia*; atretic follicles; few follicle cysts; tunica very thick.

CASE 19.—V. M., June, 1937, aged 22 years, single. *Amenorrhea of 14 months' duration*. Rectal palpation unsatisfactory. Pneumoroentgenogram showed bilateral cystic ovaries; bilateral wedge resection was done in September, 1937. Patient menstruated 3 days after operation. Last examined in February, 1938: no recurrence of cystic ovaries. Reported monthly periods of 20- to 26-day intervals. Pathology (No. 2705): Corpus luteum; many follicle cysts; primordial follicles.

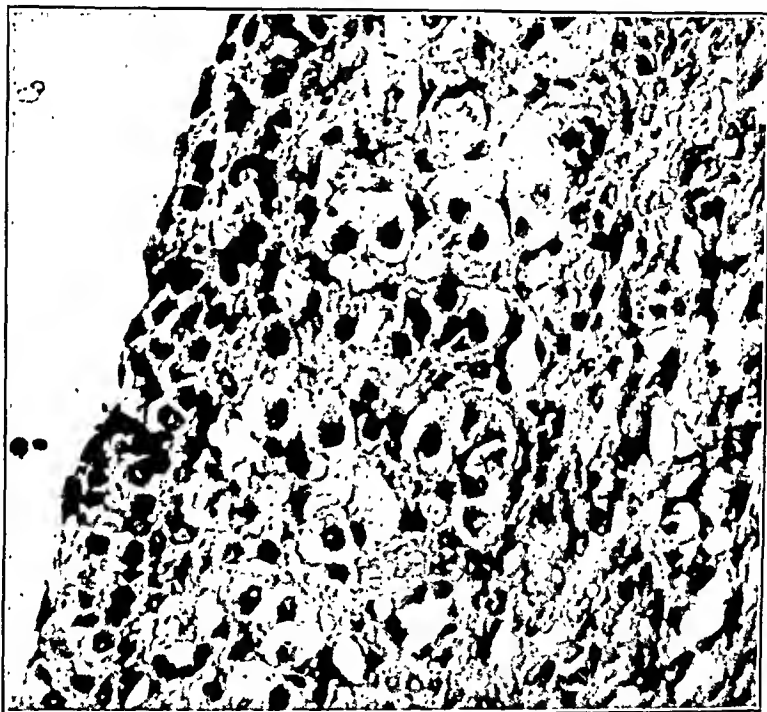


Fig. 3.—Case 20. Wall of follicle cyst showing several layers of granulosa cells and luteinized theca interna layer.  $\times 400$ .

CASE 20.—V. H., February, 1935, aged 23 years, single. *Irregular periods, 3 to 8 weeks, last period 2 months previously; pain in right lower quadrant*. Tender left ovary found in the cul-de-sac. Hirsutism marked. Exploratory laparotomy revealed bilateral polycystic ovaries and adherent appendix. Typical bilateral wedge resection and appendectomy performed. Following operation, periods were regular at 30- to 33-day intervals. In 1937, 12 periods of 25 to 31 days; in 1938, 12 periods, 24 to 32 days, usually 27. Last examined in February, 1939 at which time there was no recurrence of cystic ovaries; general health improved. Pathology (No. 265): Follicle cysts; no luteinization; several growing follicles; fairly thick tunica; large amount of theca externa in follicle cysts; thick theca interna; proliferating granulosa layer of cysts.

CASE 21.—M. M., December, 1935, aged 19 years, single. *Complained of amenorrhea*. Spotted 3 times in past 6 years; no regular menses. Profuse growth of coarse hair on cheeks and upper lip. Rectal examination unsatisfactory. Pneumoroentgenogram showed a small uterus and bilateral cystic ovaries. Bilateral wedge resection February, 1936, followed by menses in March, May, June, and July. Examination in June, 1937 showed no recurrence of cystic ovaries, the

rence of cystic ovaries. Marked improvement was noted in physical development. Breasts were developed, the hair on the face was of finer texture and much less noticeable; physical development was decidedly more feminine in type. Pathology (No. 1816): Multiple follicle cysts; no luteinization. Atrophic *Corpora albicantia*; marked proliferation of granulosa lining; normal tunica; numerous primordial follicles.

CASE 14.—M. G., April, 1935, aged 31 years, married 8 years. *Complained of sterility* and of very scant menses lasting but 1 day; regular in occurrence. Hirsutism of upper lip but otherwise feminine in type. Pelvic examination was negative. Pneumoroentgenogram in January, 1936, showed bilateral cystic ovaries and tubal obstruction. Repeat patency and pneumoroentgenogram in July, 1936, with same findings. Laparotomy, October, 1936. Both tubes were adherent but patent when tested from within; numerous small cysts were present in both ovaries. Bilateral wedge resection and lysis of adhesions were performed. Periods have improved in quality, now lasting 2 or 3 days. General health improved. In 1937, 11 periods of 23- to 26-day intervals, with one 32- and one 48-day interval. Last examined on Nov. 10, 1938, at which time there was no evidence of recurrence of cystic ovaries. Pathology (No. 3012): Beginning papillary adenofibroma on surface; several large follicle cysts; old corpus luteum; *Corpora albicantia*; recent atretic follicles; thick tunica.

CASE 15.—A. K., December, 1935, aged 23 years, married 1½ years. *Two to 3 months' amenorrhea; last period 3 months' ago; sterility.* Moderate obesity and hirsutism; masculine in type. Uterus 2 degrees retroverted; adnexa not palpable. Pneumoroentgenogram revealed the right ovary cystic; left was not visualized. Bilateral wedge resection on Feb. 19, 1936 for typical bilateral polycystic ovaries. In 1936, 10 periods, 27- and 34-day intervals, usually 29 or 30 days; 1937: periods regular, 28 to 31 days. Last examination, June, 1938: no change in hirsutism; pelvic examination revealed no recurrence of cystic ovaries. Report of urologist (Dr. A. E. Jones): Husband suffers from oligospermia. Pathology (No. 545): Luteinization of theca interna; several large follicle cysts; atretic follicles; thick tunica.

CASE 16.—E. H., September, 1937, aged 21 years, married 2 years. *Amenorrhea from 1 to 3 months; intervals becoming longer in past year.* Pain in both lower quadrants. Pelvic examination: Uterus normal in size, both ovaries cystic and tender. Bilateral wedge resection: typical bilateral polycystic ovaries. For next 9 months following operation, she menstruated at intervals of 31 to 37 days and has improved in general health. July, 1938, examination revealed no evidence of recurrence of cystic ovaries. Pathology (No. 2581): Numerous follicle cysts; thick granulosa layers; moderately thick tunica; fibrosis of ovary; atretic follicles; normal Graafian follicle.

CASE 17.—E. A., June, 1937, aged 16 years, single. Chief complaint: *amenorrhea.* Menstruated only twice since puberty. Marked hirsutism of male type which began at age of 12 and became more profuse; breasts underdeveloped. Rectal examination was negative. Pneumoroentgenogram showed a small uterus and both ovaries enlarged and cystic. Sella turcica was negative. X-ray showed no evidence of adrenal enlargement; metabolic studies were negative. Bilateral wedge resection performed in July, 1937. Patient menstruated on seventh postoperative day and again 34 days later. Amenorrhea of 4 months followed by periods at intervals of 32, 41, 43, and 121 days. Marked improvement in feminine development; breasts increased in size and facial hirsutism improved. Last examination in January, 1939: no recurrence of cystic ovaries. Pathology (No. 2070): Numerous follicle cysts; luteinization of theca interna; very thick tunica; many primordial follicles; follicle cyst undergoing luteinization of theca interna; old *Corpora albicantia*.

CASE 18.—R. B., October, 1938, aged 27 years, single. *Complained of 3 years' amenorrhea, 1934 to 1937, with pain in both lower quadrants.* Three months' amenorrhea prior to admission. Obesity, hirsutism of face, arms and legs—masculine in type. Rectal examination unsatisfactory. X-ray showed no evidence of adrenal tumor; sella turcica was negative. Pelvic pneumoroentgenogram showed the



hirsutism of face, male type, and slight obesity. Examination showed a normal uterus and typical bilateral polycystic ovaries. Bilateral wedge resection, Gilliam suspension and appendectomy were performed. Periods every 2 to 4 weeks followed and pregnancy occurred April, 1937. Porro cesarean section performed at term for severe intra-partum infection. Pathology (No. 983): Fibrosis of ovary; atretic follicles; numerous follicle cysts; *Corpora albicantia*; normal tunica; one apparently normal maturing Graafian follicle surrounded by markedly proliferating theca interna.

CASE 28.—B. R., November, 1935, aged 27 years, married. *Complained of amenorrhea of 9 months to one year.* Pelvic examination showed a small uterus, right ovary palpably enlarged and cystic; left ovary not palpable. Slight obesity. Pneumoroentgenogram showed bilateral cystic ovaries. Dilatation and curettage and typical bilateral wedge resection performed. Menses on third postoperative day.



Fig. 4.—Case 26. Atretic follicle, marked luteinization of theca interna, early luteinization of granulosa layer.  $\times 140$ .

Postoperative examination, Dec. 5, 1935: no recurrence of cystic ovaries. Did not return for follow-up. Pathology (No. 2840): Proliferating endometrium; number of follicle cysts with fairly thick tunica; atretic follicles; luteinized theca interna (Table I).

For the past three years, all of these patients were given menstrual calendar cards and each year the collected cards were exchanged for new ones; hence an accurate menstrual record was obtained. A study of these records reveals that while none of the patients menstruated at exactly twenty-eight-day intervals, they had recurring cycles within the normal variation. This observation is in complete accord with the results of our study of several hundred calendar records obtained from our clientele. We found that none of our patients were entirely regular, but that variations of 4 to 6 days were usual, and wide variations not infrequent in women who claimed to menstruate regularly.

uterus appeared somewhat larger, facial hirsutism was improved and the breasts were developed. Patient reported she was menstruating regularly; failed to return menstrual calendars for 1937 and 1938. Pathology (No. 394): Tunica very thick; granulosa cells luteinized; beginning atretic follicles with luteinization of theca interna; many large follicle cysts.

CASE 22.—P. P., May, 1937, aged 23 years, married. *Complained of 2 months' amenorrhea*; always irregular. Uterus small, tender cystic mass behind the uterus. Pneumoroentgenogram showed bilateral cystic ovaries. Bilateral wedge resection; periods regular every 31 to 32 days after operation. Patency test, March, 1938 followed by pregnancy and delivery at term. Postnatal examination, March, 1939 revealed normal pelvic status with no recurrence of cystic ovaries. Pathology (No. 1387): Many follicle cysts; fairly thick tunica; many *Corpora albicantia*.

CASE 23.—G. S., August, 1929, aged 23 years, married. *Complained of a 3 months' amenorrhea*. Bilateral cystic ovaries on palpation confirmed by pneumoroentgenogram. Laparotomy: right dermoid cyst and left polycystic ovary. Bilateral wedge resection, following which for 6 years, periods were regular at 30- to 32-day intervals. Patient practiced contraception during this time. Upon omitting same, she promptly conceived (March, 1935) and delivered at term. Examination in November, 1937 showed a normal pelvic status with *no recurrence of cysts—8 years after resection*. Menses every 28 to 35 days in 1937, and in 1938, 28- to 34-day intervals, with one interval of 43 days. Pathology (No. 1331): Right ovary, many *Corpora albicantia*; follicle cysts; dermoid cyst; left ovary, numerous follicle cysts; normal tunica.

CASE 24.—L. S., September, 1936, aged 23 years, married 3 years. *Complained of 2 years' amenorrhea*. Hormone therapy of no benefit. Slight hirsutism. Pelvic findings indefinite. Pneumoroentgenogram showed bilateral cystic ovaries with globular right ovary. Subsequent examination followed by vaginal bleeding; second pneumoroentgenogram revealed diminution in size of globular swelling on right. Both ovaries were still cystic. Wedge resection was performed. Regular periods every 26 to 29 days, usually 27, through 1936 and 1937. Pregnancy occurred in December, 1937, with delivery at term. Postnatal examination, October, 1938: no evidence of recurrence of cystic ovaries. Pathology (No. 2692): Numerous follicle cysts; luteinized theca interna; *Corpora albicantia*; atretic follicles; primordial follicles; thick tunica; corpus luteum.

CASE 25.—S. W., July, 1935, aged 23 years, married 2½ years. *Complained of sterility* with somewhat irregular periods. Unsatisfactory pelvic findings. Pneumoroentgenogram revealed bilateral cystic ovaries. Bilateral wedge resection performed, following which periods were every 24 to 28 days. Last examination, August, 1936: normal pelvic status with no recurrence of cystic ovaries. Male sterility factor: Failure of intromission; unsuccessful operation for hypospadias. Pathology (No. 1048): Luteinization of theca interna; numerous follicle cysts; fairly thick tunica; many atretic follicles; few *Corpora albicantia*; primordial follicles.

CASE 26.—M. W., July, 1935, aged 28 years, married 6 years. *Complained of sterility and irregular periods with 2 months' amenorrhea*. Left ovary palpably enlarged and tender. Pneumoroentgenogram showed bilateral cystic ovaries. After typical wedge resection, patient had four periods at intervals of 28, 29, 34, and 48 days, and then became pregnant with delivery at term. Postnatal examination showed no recurrence of cystic ovaries. In 1937, patient had 7 periods, 28- to 33-day intervals; in 1938, 28 to 36 days, with one interval of 46 days. Pathology (No. 36P44): Corpus luteum with hemorrhage; many *Corpora albicantia*; fibrosis of ovary; atretic follicles with luteinization of granulosa and theca interna cells; marked proliferation of theca cells; normal tunica.

CASE 27.—A. M., May, 1931, aged 24 years, married 3 years. *Complained of sterility and amenorrhea of 2 years and 8 months*; always irregular and scant. Two previous periods of amenorrhea each lasting one year. Pain in right lower quadrant,

TABLE II. PATHOLOGY

CASE	THICK TUNICA	GRAAFIAN FOLLICLES	FOLLICLE CYSTS	CORPUS LUTEUM	CORPORA ALBICANTIA	LUTEINIZED THECA	OTHER FINDINGS
8	Normal	++	++	Cyst	0	0	
9	+	0	++	Old	+	+	Fibrosis
10	++	+	++	0	0	++	Endometriosis
11	++	0	++	0	0	+	Fibrosis
12	Normal	0	++	0	++	+	
13	Normal	++	++	0	++	0	
14	++	0	++	Old	+	0	Papillary adenofibroma
15	++	+	++	0	0	+	
16	++	++	++	0	0		Fibrosis
17	++	++	++	0	Old	+	
18	++	0	+	0	+	0	Fibrosis
19	Normal	++	++	Cyst	+	0	
20	+	++	++	0	0	0	Proliferating theca interna
21	++	0	++	0	0	+	
22	+	0	++	0	++	0	
23	Normal	0	++	0	++	0	Dermoid
24	++	++	++	Old	+	+	
25	+	++	++	0	+	+	
26	Normal	0	++	Hemor-rhagic	++	++	Fibrosis
27	Normal	+	++	0	+	0	Fibrosis
28	++	0	++	0	0	+	

## TREATMENT

Amenorrhea is a symptom and as such is evidence of the disturbed physiologic function of the sex apparatus. In the early stages, it may be due to hormonal disturbances in which no definite pathologic lesion may be demonstrated in the sex organs. In fact, both amenorrhea and uterine bleeding, according to B. Zondek,<sup>3</sup> are due to the same fundamental process; namely, a hypersecretion of the anterior lobe of the pituitary gland. When, however, in the opinion of the authors, such dysfunction persists for a long time, histologic evidence appears in the ovary in the form of multiple follicle cysts varying in size from a few millimeters to more than one centimeter. When this pathologic change has occurred, amenorrhea and sterility are the chief symptomatic characteristics and pain is an occasional accompaniment.

Many contributions have appeared in the literature on the medical and surgical treatment of ovarian dysfunction. It is our belief that the good results reported from medical management, such as glandular and radiation therapy, have been obtained in patients in whom the ovarian dysfunction is still in the stage where no demonstrable enlargement of the ovary is found. Since none of the reports of successful treatment by these methods include patients in whom definite polycystic ovaries were demonstrated, those conditions must be regarded as purely dysfunctional. It seems evident, then, that patients who have failed to respond to medical treatment and have developed definite pathologic lesions in the ovary require surgical intervention.

TABLE I. CASE ANALYSIS

NO. CASES	STATUS	AMENOR-RHEA	STERILITY	PALPABLE CYSTIC OVARIES	PNEUMO-ROENT-GENO-GRAM	HIRSUTISM	PAIN	HORMONE TREAT-MENT
10	Single	9		3—both 1—one 6—none	9	7	2	1
18	Married	16	14	5—both 6—one 7—none	15	8	5	7

## PATHOLOGY

The pathology in the 21 additional cases was found to follow a similar pattern to that described in our previous publication. Grossly, each ovary was enlarged 4 to 5 times and was either elongated or globular, and contained numerous small cysts in the cortex. The capsule was thick and leathery with variations in thickness in different portions of the section. Occasionally, a larger follicle cyst found protruding from the surface of the ovary was covered by a thin capsule, giving the ovary a lobulated appearance. Upon section of the ovary, a clear fluid was released under pressure from numerous small cysts measuring from 2 to 15 mm. in diameter. Usually these cysts were limited to the cortex but in some instances involved the hilus. Not infrequently, a corpus luteum cyst was found in addition.

Microscopically, the most characteristic finding is the numerous follicle cysts. In our previous publication, we differentiated between theca-lined and granulosa-lined cysts, but we now believe this differentiation to be of no significance. The smaller cysts are all lined with multiple layers of granulosa cells. As the cysts enlarge, the granulosa lining becomes thinned out until but a single layer is present. The largest cysts seem to have lost the granulosa layer. This may either be due to an artifact in sectioning or to actual pressure atrophy. However, physiologically, the theca cells as well as the granulosa cells are estrin-producing so that the actual differentiation between such cysts is of no clinical importance.

A thick fibrous capsule is characteristic and is usually associated with increased fibrosis of the ovary and hyperplasia of the theca layers. The latter is most evident surrounding the atretic follicles which are observed to be more numerous than in the normal ovary. Robinson<sup>2</sup> called attention to the presence of luteinization of the theca interna of such atretic follicles and stated that this was a characteristic finding in patients with metrorrhagia. Further study of our sections reveals that it is equally characteristic in the ovaries of our patients with amenorrhea. The luteinization not only involves the theca interna but occasionally the granulosa layer of atretic follicle cysts as well (Figs. 3 and 4). We have no knowledge as to whether such luteinized cells are capable of producing progesterone. Table II is a detailed analysis of the sections in each case of this series.

resulted from this procedure and that in 13 of the 17 patients, regular menses were established. Pregnancy resulted in one case. Bailey believed that the pathologic change which occurs in the ovary is a result of the presence of a basic pituitary hormone deficiency; that lack of the follicle ripening and ovulation leads to development of multicystic disease with chronic thickening of the tunica; that the more mature follicles are probably destroyed intrinsically or by pressure obliteration, and the younger, deeper ones are mechanically prevented from reaching the surface to mature and ovulate. This interpretation of the mechanics involved in the lack of ovulation is in accord with the view expressed in our previous communication. The technique which he employs attempts to assist to maturity the remaining follicles by facilitating their approach to the surface. A single ovulation, he states, is capable of re-instating the normal ovular rhythm. He justifies the operation with the belief that when the pathologic condition can be diagnosed, the prospect of a spontaneous return to normal function is remote, inasmuch as the lesion is a progressive one. We are in accord with the principles involved in Bailey's mode of therapy, disagreeing only with the technique which he employs.

Robinson,<sup>2</sup> after prolonged study, was convinced that patients suffering from hypo- or hyperfunction of the ovary for long periods will present, on careful bimanual examination, enlargement of one or both ovaries. If endocrine therapy and dilatation and curettage have failed to relieve bleeding, ovarian partial resection is indicated. He reports 4 such cases, utilizing a technique of wedge resection and suture similar to that described by us. Normal menses were restored in all 4 patients and pregnancy resulted in 2. He likewise reported 3 cases of amenorrhea treated by the same method, in which the menses were successfully regulated, with pregnancy occurring in 2. In both conditions he concludes that removal of the cystic cortex of the ovary restores the normal pituitary-ovarian relationship. Robinson enters into a thorough discussion of this involved endocrine problem which may be reviewed with profit.

Reycraft,<sup>12</sup> after encountering disappointing results with endocrine treatment, noted the gratifying effects of wedge resection reported by Robinson, and utilized this principle in treating 6 cases. He, however, modified the technique by performing a "decortization" of the ovary rather than a wedge resection, believing that the thick tunica was the significant barrier to ovulation. After removing a portion of the ovarian cortex, he obtained hemostasis by means of a mattress suture of fine catgut, leaving the ovaries denuded of their normal covering. He obtained restoration of the menstrual function in 5 of the 6 cases of amenorrhea, and pregnancy resulted in one case.

Stein and Leventhal<sup>1</sup> in 1935 reported 7 cases of amenorrhea associated with bilateral polycystic ovaries in whom bilateral wedge resection was performed. A large wedge of from one-half to two-thirds of the ovarian cortex was removed and the deeper cysts in the remaining portion of the ovary were punctured. The ovary was then closed by means of a single suture of fine catgut in two layers, the first, a deep hemostatic stitch locked at either end, and returned as a superficial approximating suture. This left an ovary of approximately normal size and appearance. There was restoration of the menses in all of the 7 patients, pregnancy occurring in 5 patients, twice in 3 of them. A follow-up on 6 of the 7 patients was obtained by the present authors and appears in the history abstracts above.

We desire to add to this group 21 patients, all of whom complained of amenorrhea and/or sterility, and in whom bilateral ovarian enlargement was either found by palpation or demonstrated by pneumoroentgenography. As will be seen in Table III, the combined series consists of 10 single and 18 married women. Postoperatively, regular menses were restored in 23; irregular periods occurred in 2, and follow-up was unsuccessful in 3. One single girl in the first series was subsequently married and gave birth to a child at term. In addition to this case, 10 of the married group became pregnant, 4 of them twice. These patients were followed to date by means of menstrual calendar records and periodic pelvic examinations. No recurrence of cystic ovaries was detectable upon postoperative and follow-up examination in any case, 7 patients having been followed for more than five years (3, 5 years; 3, 8 years; 1, 9 years) (Table III). It would be desirable for scientific purposes

*Medical Management.*—Hormone therapy has been employed in the past few years for early dysfunction exhibiting amenorrhea and often associated with sterility, but with very disappointing results. Estrogenic substances have been employed, but according to Frank,<sup>4</sup> they serve no useful purpose in this condition. The pregnancy urine extract has likewise been used with unsatisfactory results. We question whether therapy with pregnancy urine extracts, mare's serum hormone and extracts of the anterior lobe of the hypophysis is justified for these conditions, for not only are they of dubious value, but may actually intensify the pathologic change in the ovary. In cases of hypothyroidism associated with sterility, thyroid extract has been shown to be of definite therapeutic value. Tamis<sup>5</sup> declares that a combination of thyroid and roentgen therapy is the best agent for stimulating menstruation in cases of functional amenorrhea and in 60 per cent of his 25 cases, the menses were restored by this means.

Perhaps one of the most useful forms of medical treatment of functional amenorrhea and sterility is radiation therapy, which Rubin<sup>6</sup> recommended in 1926, when he reported a successful series of cases. More recently, Kaplan,<sup>7</sup> basing his opinion on his experience with 128 women so treated over a period of twelve years, declared that no other method of treatment so far devised, including hormone therapy, has yielded results as satisfactory or equally as good. In 76 patients, the menses were regulated by treatment and 52 failed to respond; all of the patients had previously been treated with endocrine preparations without success. Radiation was applied to the ovaries in all cases, to the pituitary as well in 80, and in 5, to the thyroid also. Forty-four women became pregnant, giving birth to 47 living children. Kaplan was able to follow up 114 of his patients. However, there is no detail concerning postradiation pelvic examination to determine whether palpable ovarian pathology developed; nor is there evidence in this report that any of the patients so treated had bilateral polycystic ovaries prior to radiation therapy.

Mazer and Spitz<sup>8</sup> likewise used low dosage radiation in the treatment of 48 women complaining of secondary amenorrhea, 22 of whom menstruated regularly for one year or more thereafter. Of the 103 sterility patients so treated, 22 conceived. The authors state, however, that but 38 of the women were married to fertile mates.

Friedman and Seligman<sup>9</sup> treated 9 cases of amenorrhea, diagnosed as basophilic adenoma of the hypophysis, with x-ray of the pituitary and ovary; there was restoration of the menses in all and occurrence of pregnancy in 3 cases. Likewise, in these cases there is no evidence that any of the foregoing had polycystic ovaries prior to treatment.

It is erroneous to call x-ray a stimulating agent, for its action is always destructive, according to Tamis;<sup>5</sup> destruction of the inhibitory forces results in stimulating effects. Israel<sup>10</sup> declares that while radiation is purely an empiric measure, it is safe in experienced hands. It is our opinion that the favorable results which have been obtained with roentgen therapy have occurred in cases of endocrine dysfunction which have not yet reached the stage where fixed changes have taken place in the ovary.

No one has reported treating polycystic ovaries with x-ray. When both ovaries are found to be polycystic, either upon pelvic bimanual or roentgen visualization, we believe that surgical treatment is indicated.

*Surgical Treatment.*—Since our previous report on this subject in 1934, there have been a number of interesting papers bearing on the surgical treatment of bilateral polycystic ovaries. All of these communications have been based upon the same principle, namely, the removal of a portion of the cystic cortex or evacuation of the cystic follicles. However, different techniques have been employed for this purpose with uniformly good results.

Bailey<sup>11</sup> in 1937 described the operation of "extroversion of the ovary for functional amenorrhea" and reported his results in 17 patients observed over a period of six years. All of his patients had previously been treated with hormone therapy without improvement. He therefore removed a wedge of each ovary and sutured each half of the slit gonad so that it remained wide open and turned the raw surfaces into the cul-de-sac to prevent adhesions. He declared that no complications

4. The calendar method of recording menstrual cycles was utilized in all of these patients in the past three years so that accurate data are available.

5. Menstruation was restored in 25 of the 28 women and in 3 there was no follow-up. Of 19 married women (one single when operated upon and subsequently married), 11 became pregnant, with a total of 15 pregnancies. In this group were 14 who complained primarily of sterility and of these, 8 became pregnant.

6. Follow-up pelvic examinations were made routinely and no case of recurrent cystic ovaries has been observed. Seven patients have been followed for from five to nine years since operation.

7. On the basis of our long period of study of this condition, and the results obtained in the 28 women herein reported, we recommend that surgical treatment be considered the method of choice for bilateral polycystic ovaries associated with amenorrhea and/or sterility. The technique of partial oophorectomy by wedge resection and suture is advocated.

We wish to express our gratitude for assistance in the preparation of the material for this paper to Drs. M. L. Leventhal and Otto Saphir.

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#### DISCUSSION

DR. JOHN I. BREWER.—I believe that the paper demonstrates that surgical procedure is of value in certain cases of amenorrhea. The long follow-up shows that surgical removal of some ovarian tissues in these instances does cause improvement. We have operated upon 6 such patients in the last five years. Of these 6 one is two months pregnant at the present time.

In contrast to Stein and Cohen's paper in which the treatment described is for secondary amenorrhea, we have one patient, 22 years old, who had a primary amenorrhea and who after extensive endocrine therapy failed to flow. By extensive therapy, I mean 200,000 to 300,000 units of theelin in three weeks and 30 mg. of proluton in ten days. This patient was found at operation, not to have polycystic ovaries but fibrous appearing ovaries. These were biopsied by a technique similar to the authors' and demonstrated small cystic follicles, none of which contained ova. Most of them showed luteinization of the theca without luteinization of the granulosa. Three days following curettage in which very little endometrial tissue was obtained, the patient flowed for two days. She was operated upon in 1934, and in the five years since has menstruated every month with one exception of a sixty-day period of amenorrhea. As for the other four patients we have had, they have improved but since all four are single we have no data as to sterility.

Other methods of treatment that have been suggested, such as puncture of the cysts and vaginal massage of the ovaries, have one feature in common, trauma. Such trauma would certainly increase the blood supply, which physiologically any organ needs for increased function.

to substantiate, by follow-up, the bimanual findings with pneumoroentgenograms as was done preoperatively. However, as these patients were all in good health, menstruating regularly, many of them having borne children, there was no justification from the standpoint of the patient for the additional expense and inconvenience. All of these patients are now in good health and calendar records of their menses are recorded in the case histories above.

Many surgeons are accustomed to treating polycystic ovaries incidentally found at laparotomy by multiple puncture of the follicle cysts. Recently, Zondek<sup>3</sup> has advocated the performance of such multiple puncture through the cul-de-sac, thus obviating the necessity for laparotomy. He reported success with 40 cases.

TABLE III. RESULTS

NO. CASES	STATUS	AMENOR-RHEA	STERILITY	MENSES—P.O.		NO. PTS. PREG-NANT	TOTAL PREG-NANCIES	RECUR-RENCE
				REG.	IRREG.			
10	Single	9		7	1 2†	1*	1*	0
18	Married	16	14	16	1 3†	10§	14	0‡
28		25	14	23	2	11	15	0

\*Married 4 months after operation.

†No follow-up.

‡7 cases followed 5 to 9 years without recurrence.

§8 of 10 patients complained primarily of sterility.

Although four separate surgical methods of treating polycystic ovaries have been described, it is noteworthy that success in restoring the physiologic function of the ovary was obtained in each. It is obvious that the good results were due to the removal of cortical follicle cysts—the significant lesion in the relationship between polycystic ovaries and the dysfunction. While the methods varied, the results were uniformly good. In our opinion, Zondek's cul-de-sac puncture of the follicle cysts appears to be too inadequate and uncontrolled for general use. The procedures of both Bailey and Reycraft, based on the assumption that the thick tunica is the significant barrier to ovulation, leave the ovaries denuded of their normal epithelium, thus inviting postoperative bleeding and adhesions. On the other hand, wedge resection and suture, which was described by the authors and also employed by Robinson, is a complete surgical technique which restores the normal anatomy of the ovary. Contrary to a common prejudice, this operation is not followed by recurrence.

#### SUMMARY AND CONCLUSIONS

1. During the past ten years, we have operated upon 28 patients with bilateral polycystic ovaries in whom amenorrhea and/or sterility were the chief characteristics.

2. Pneumoroentgenography was found to be of distinct value in diagnosis. Bilateral ovarian enlargements were demonstrated by this means in cases where pelvic examination was unsatisfactory and was corroborative in others. This form of x-ray diagnosis was employed in 24 of our 28 cases.

3. Bilateral partial oophorectomy by means of wedge excision and suture was found to be a satisfactory technique.



anterior pituitary inhibition. Moreover, progestin produced by corpora lutea, corpus luteum cysts, or possibly from luteinized atretic follicles (false corpora lutea) would produce amenorrhea.

In answer to Brewer's statement about vaginal trauma producing pelvic hyperemia, it seems to us more logical to suppose that it would produce follicle rupture and thus cure the amenorrhea.

Allen suggested cul-de-sac resection. We have felt that the cul-de-sac route was not safe because of the great possibility of hemorrhage and therefore in all of our cases, we used the abdominal route.

## FAMILY TRENDS ACCORDING TO ECONOMIC STATUS

CHARLES P. SHELDON, M.D., BOSTON, MASS.

**A**LTHOUGH human fertility is altered by social status, occupation, urbanization, education, religion, biologic factors, etc., the economic situation is of considerable importance in determining the size of a family. We have witnessed during the past several years the effects of an economic depression during which large numbers of persons have had their mode of living disrupted. Family incomes are in many instances low and the relief rolls are enormous. The social implications of this situation are brought out by a study of fertility rates in groups of persons of varying economic levels.

### FERTILITY RATES

The present study is based upon records of 964 women who were delivered at the Albany Hospital, Albany, New York, in the years 1931 to 1935 inclusive. These were subdivided in three main groups. The service group was made up of city and ward patients who were largely supported by public funds. A semiprivate group consisted of patients of moderate means. The private group was made up of persons who were financially independent. The patients were from rural as well as urban districts.

Table I shows the number of pregnancies these women have had. The average number of pregnancies for the three groups combined was 2.4. Those in the service group (city and ward) had an average of 3.4 pregnancies and those in the self-sustaining group (semiprivate and private) had an average of 2 pregnancies.

TABLE I. PREGNANCY INCIDENCE ACCORDING TO ECONOMIC STATUS

TYPE OF SERVICE	NUMBER OF MOTHERS	NUMBER OF PREGNANCIES	AVERAGE NUMBER OF PREGNANCIES
Total	964	2,314	2.4
City and ward	262	895	3.4
Semiprivate	376	775	2.1
Private	326	644	2.0
Private and semiprivate	702	1,419	2.0

In order to eliminate the differences of age in the various groups, calculations were made for the number of months each woman could have

Another probable factor is the estrogenic concentration. It has been demonstrated experimentally that certain maintained levels of estrogenic substance can produce ovarian inactivity, presumably by way of the pituitary. If this quantitative level is changed, then menstruation ensues. The work done by Stein and Cohen suggests that it is the change in quantitative estrogenic level that brings about more normal menstruation.

In conclusion, I wish to say, as the authors have stressed, that this procedure is not a cure-all for amenorrhea or sterility. In other words, every patient with amenorrhea and sterility should not be operated upon. The operation should be done only in selected instances.

DR. EDWARD ALLEN.—I would like to report a further case. This patient was 24 years old and had never menstruated. She was very masculine, with large clitoris which she came to have removed. The ovaries were less than one-third normal size and the uterus so small that you could hardly tell whether you were feeling a wedge of peritoneum. I removed a wedge from each ovary. Whereas, when we first examined her you could not put the smallest probe in the cervix, within three weeks a Hegar dilator could be passed. She has since married, and the uterus is now two-thirds normal size.

Certainly this set of ovaries has very little follicular activity, which brings up the question of puncturing through the cul-de-sac. By puncturing through the cul-de-sac you can cut down on the hospitalization and discomfort. I have resected two cases in the last year through the cul-de-sac, which were of the polycystic type. I think it is important to consider this method and rather than treat too few, treat more of these cases surgically.

DR. A. M. SCHWITTAY, MADISON, Wis.—I would like to ask whether in these cases basal metabolism determinations have been done. It is our experience that in many amenorrheic cases there is a low basal metabolism. We have found in many young girls, particularly those who have menstruated for a time and then have amenorrhea, a deficient thyroid is at fault.

DR. M. L. LEVENTHAL.—In the past year I have had occasion to operate upon three cases with polycystic ovaries, to study the endometrial biopsies, and to take basal metabolic rates. I found in all three that the biopsy showed a pre-ovulatory or a proliferative endometrium. In two of the cases that were typically polycystic, in that they had long periods of amenorrhea and menstruated normally after operation, the basal metabolic rates were normal. In one it was minus 31. This patient was given intensive thyroid therapy and the basal metabolic rate came up to minus 1 and still she did not menstruate. In this patient only by pneumoperitoneum were we able to discover the polycystic ovaries. We operated upon these two patients and both menstruated within the month, one on the twenty-eighth and one on the twenty-ninth postoperative day. I think the role of hypothyroidism in amenorrhea is important, but not in the presence of these organic changes in the ovary.

DR. COHEN (closing).—There are many theories concerning the cause of polycystic ovaries. Of these, two merit attention, namely, the mechanical theory wherein the thickened tunica albuginea prevents follicle rupture, and the theory of hyperpituitarism. In animals, anterior pituitary extracts and implants, anterior pituitary-like hormone, as well as the mare serum hormone will produce cystic ovaries. In the human being, mare serum hormone in large doses will produce cystic ovaries. In the newborn infant, Spivack reported the occurrence of cystic ovaries, produced perhaps by the high level of maternal prolactin. Cushing and Kraus have reported cases of increased intracranial pressure associated with polycystic ovaries. The finding of polycystic ovaries at prepuberty and menopause may be considered physiologic. Perhaps in the menopause the increased prolactin A might be a factor.

The occurrence of amenorrhea may be explained by the failure of follicle rupture because of mechanical crowding. The estrin produced by follicle cysts may produce

TABLE IV. MISCARRIAGE RATES ACCORDING TO ECONOMIC STATUS

TYPE OF SERVICE	NUMBER OF PREGNANCIES	NUMBER OF MISCARRIAGES	NUMBER OF MISCARRIAGES PER 1,000 PREGNANCIES
Total	2,314	39	16.9
City and ward	895	22	24.6
Semiprivate	775	11	14.2
Private	644	6	9.3
Private and semiprivate	1,419	17	12.0

TABLE V. STILLBIRTH RATES ACCORDING TO ECONOMIC STATUS

TYPE OF SERVICE	NUMBER OF PREGNANCIES	NUMBER OF STILLBIRTHS	NUMBER OF STILLBIRTHS PER 1,000 PREGNANCIES
Total	2,314	57	24.6
City and ward	895	27	30.2
Semiprivate	775	16	20.6
Private	644	14	21.7
Private and semiprivate	1,419	30	21.1

TABLE VI. PREGNANCY WASTAGE RATES ACCORDING TO ECONOMIC STATUS

TYPE OF SERVICE	NUMBER OF PREGNANCIES	TOTAL NUMBER OF PREGNANCIES WASTED	PREGNANCY WASTAGE RATE PER 1,000 PREGNANCIES
Total	2,314	275	118.8
City and ward	895	180	145.3
Semiprivate	775	72	92.9
Private	644	73	113.4
Private and semiprivate	1,419	145	102.2

TABLE VII. INFANT MORTALITY RATES ACCORDING TO ECONOMIC STATUS

TYPE OF SERVICE	NUMBER OF LIVE BIRTHS	NUMBER OF INFANT DEATHS	INFANT MORTALITY RATE PER 1,000 LIVE BIRTHS
Total	2,012	122	60.6
City and ward	740	70	94.6
Semiprivate	703	20	28.4
Private	569	32	56.2
Private and semiprivate	1,272	52	40.9

TABLE VIII. INFANT SURVIVAL RATES ACCORDING TO ECONOMIC STATUS

TYPE OF SERVICE	NUMBER OF PREGNANCIES	NUMBER OF SURVIVING INFANTS	NUMBER OF SURVIVING INFANTS PER 1,000 PREGNANCIES
Total	2,285	1,890	827.1
City and ward	868*	670	771.9
Semiprivate	775	683	881.3
Private	642*	537	836.4
Private and semiprivate	1,417	1,220	861.0

\*The results of the last pregnancy for 27 of the city and ward group and 2 of the private group were unknown.

become pregnant.<sup>1</sup> This number of months was obtained by determining the interval between marriage and last delivery and subtracting 10.5 months for each live or stillbirth. Miscarriages and abortions were adjusted by subtracting the number of months pregnant plus 1. On this basis Table II was constructed, showing that although the average interval between delivery and succeeding pregnancy for the service group was only 12.5 months, the interval for the self-sustaining group was 22.4 months.

TABLE II. PREGNANCY RATES ACCORDING TO ECONOMIC STATUS.  
CALCULATIONS BASED ON EXPOSURE TO PREGNANCY

TYPE OF SERVICE	NUMBER OF MONTHS OF EXPOSURE TO RISK OF PREGNANCY	NUMBER OF PREGNANCIES	AVERAGE INTERVAL BETWEEN DELIVERY AND SUCCEEDING PREGNANCY (MONTHS)
Total	42,968	2,314	18.6
City and ward	11,206	895	12.5
Semiprivate	16,799	775	21.7
Private	14,963	644	23.2
Private and semiprivate	31,762	1,419	22.4

The statistics of this study are substantiated by similar investigations which reveal an inverse relationship between economic status and differential fertility.<sup>2, 3</sup>

Although fertility apparently increases as social status and the family income diminish, there are other factors which influence the size of a family. Reproductive wastage counteracts fertility and tends to increase, both in the individual and in the group, with an increase in fertility.

#### PREGNANCY WASTAGE

Tables III, IV, and V give the number of abortions, miscarriages and stillbirths and the rates for each per 1,000 pregnancies in the three groups. The rate in each case is much higher for the service group than for the self-sustaining group.

TABLE III. ABORTION RATES ACCORDING TO ECONOMIC STATUS

TYPE OF SERVICE	NUMBER OF PREGNANCIES	NUMBER OF ABORTIONS	NUMBER OF ABORTIONS PER 1,000 PREGNANCIES
Total	2,314	179	77.4
City and ward	895	81	90.5
Semiprivate	775	45	58.1
Private	644	53	82.3
Private and semiprivate	1,419	98	69.1

The total effect of reproductive wastage is shown in Table VI in which abortions, miscarriages, and stillbirths are added together and the rates per 1,000 pregnancies given.

The survival of children is of equal importance with the rate at which they are born. Although the infant mortality rate in the service group was 94.6, the rate for the self-sustaining group was only 40.9, which is less than one-half the rate for the service group.

## VITAMIN A DEFICIENCIES IN PREGNANCY\*

WITH CASE REPORTS ON TWO UNUSUALLY SEVERE EXAMPLES

WILBUR A. RICKETTS, M.D., F.A.C.S., DAYTON, OHIO

EXPERIMENTS have indicated that while pregnancy is a normal physiologic process, it makes additional demands on the maternal organism from the standpoint of nutrition. These experiments have indicated, for instance, that a vitamin A intake adequate under other conditions may fail to meet the increased requirements during pregnancy.

Garry and Stiven<sup>1</sup> point out that both lactation and pregnancy thus may be considered efficiency tests and that dietary deficiencies in a population are more likely to manifest themselves more clearly in pregnant and nursing women than in the general adult population.

Jeans and Zentmire,<sup>2</sup> Jeghers,<sup>3</sup> Park,<sup>4</sup> and Youmans and Corlette<sup>5</sup> have reported on the new instrument and technique which give data in relation to the vitamin A status of the subject tested.

Jeghers<sup>3</sup> has also shown correlation between this test† when the vitamin A content of the diet was very much reduced. During this experiment the dark adaptation curve was progressively impaired until subjective night blindness was produced.

The observations of Maxwell,<sup>6</sup> Green,<sup>7, 8</sup> and Moore<sup>9</sup> suggest the importance of an adequate intake of vitamin A during pregnancy.

While several reports have appeared in connection with the biophotometer tests of children, medical students, and other medical surveys, none of the reports has been in relation to the vitamin A status by means of this clinical test during pregnancy.

The biophotometer tests herein reported‡ were made using the regular technique as described by Jeans<sup>2</sup> and others, but in a few instances the test was shortened to thirteen minutes, obtaining the first light threshold which is obtained twenty seconds after the bleaching light is turned off. While this reading does not give the complete dark adaptation curve, experience has shown that it is useful in selecting the most severe cases. The complete curve was made on all severe cases reported.

The cases reported are all private patients, financially able to secure all the needed food and care. They included dietitians, nurses, and other professional women. Several were the wives of physicians or dentists. The average age of the group was 29 years, ranging from 20 to 49 years.

Jeans<sup>2</sup> has suggested that a reading of 0.6 millifoot candles twenty seconds after the bleaching light is turned out, be used as a dividing line between the normal and borderline cases. Youmans and Corlette<sup>5</sup> suggest 0.7 millifoot candles for adults. Jeghers did not attempt to set any particular limit, but divided the medical students in his survey into three groups.

\*Presented in part before the Clinical Conference, Miami Valley Hospital, Oct. 22, 1937.

†Biophotometer.

‡These tests were made through the cooperation of Dr. Ira O. Park of Dayton.

The combined effect of pregnancy wastage and infant mortality is brought out in Table VIII which shows the number of infants surviving the first year of life per 1,000 pregnancies. A thousand pregnancies in the service group produced 772 infants one year old, while 1,000 pregnancies in the self-sustaining group produced 861 surviving infants.

Although pregnancy wastage and infant mortality counteract increased fertility and tend to stabilize the size of the family, they are in themselves costly processes. Abortion alone is an enormous problem.<sup>4</sup>

#### SUMMARY AND CONCLUSIONS

1. Fertility rates for 964 women have been analyzed.
2. There is an inverse relationship between size of family and economic status.
3. The average interval between delivery and succeeding pregnancy for the group supported by public funds was 12.5 months while the interval for the self-sustaining group was 22.4 months.
4. Reproductive wastage (abortions, miscarriages, and stillbirths) and infant mortality are highest in the low-income group in which fertility is greatest.
5. One thousand pregnancies in the group supported by public funds produced 772 infants one year old while 1,000 pregnancies in the self-sustaining group produced 861 surviving infants.
6. Greater reproductive wastage and a higher infant mortality rate partially compensate for the increased incidence of reproduction in the low income group.

The author is indebted to Jacob Yerushalmy, Ph.D., Albany, New York, for his analysis of the statistics presented in this paper.

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Defendi, Stefano: *The Amino-Acid Curve in the Blood of Women with Tumors of the Uterus and of the Ovary*, *Folia gynae.* 25: 392, 1938.

The author studied the function of the liver in 44 patients with tumors of the uterus or ovary in women who had no evident functional liver alteration. The amino acid curve of Bufano was employed, which, in his opinion, is a most sensitive test for the determination of the deaminization power of the liver. Studies were made prior to operation and on the second, fifth, and ninth days postoperative. In 75 per cent of the cases a slight hepatic alteration was found. During the first forty-eight hours postoperative, there is an alteration of the amino acid curve, which is diminished in five days and returns, almost always, to normal in nine days. The manifestations, which are not very severe and transitory, were found to be directly proportionate to the severity of the operative procedure and the type of anesthesia employed. More profound changes were found when chloro-ether was used and less with novocaine.

MARIO A. CASTALLO.

This patient improved in every way following the addition of carotene in oil to a balanced diet. Headache, night blindness, and photophobia disappeared in one month, and the patient resumed all usual activities. Patient weighed 114 pounds on March 26, 1937, and on Sept. 24, 1937 had gained 20 pounds. Delivery was normal, patient had ample lactation, and felt fine.

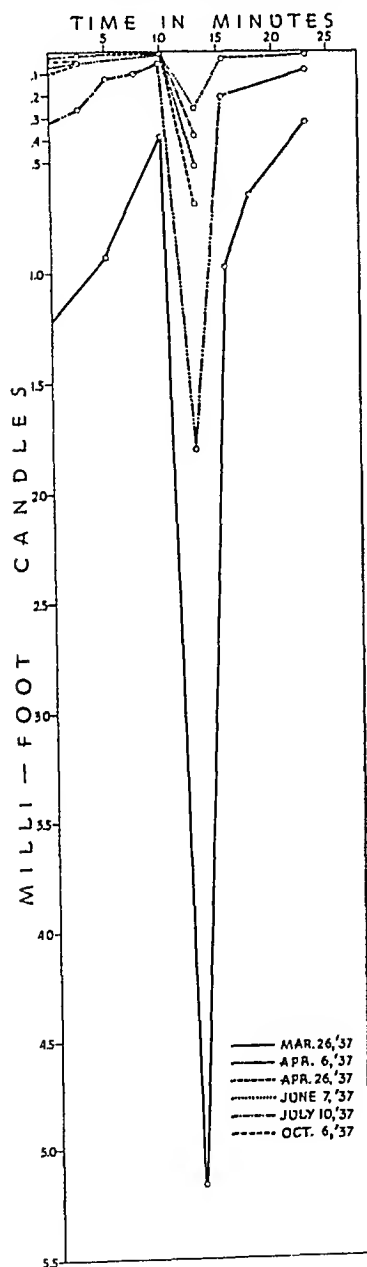


Fig. 1.

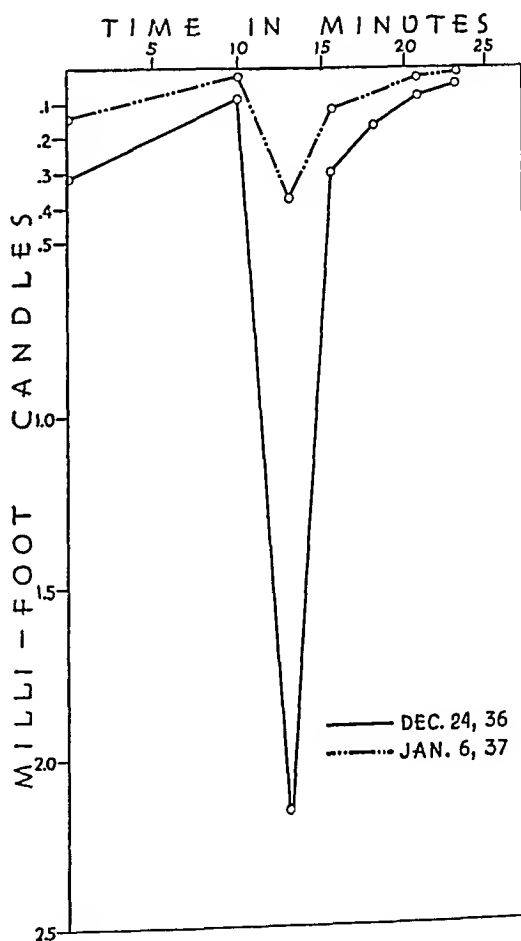


Fig. 2.

Fig. 1.—Biophotometer test curves on Case 1.

Fig. 2.—Biophotometer test curves before (lower curve) and after (upper curve) carotene in oil therapy of uncomplicated vitamin A deficiency during pregnancy.

CASE 2.—(No. 87.) Mrs. E. O., aged 20 years, white. Last menstruation Dec. 15, 1936. As a child had pneumonia. Mother reports she was the only child and had always been a problem due to dietary irregularities. Patient worked in a downtown department store as a clerk until May 10, 1937. At that time she came to the office with the following symptoms: Marked light sensitiveness, exhaustion, nausea and vomiting, blurring of vision and night blindness, clouded mentality, and headache.

For the purpose of roughly dividing this small series into groups, those ranging from 1 millifoot candle were classed as good, between 2 and 1 millifoot candles, as fair, between 3 and 2 millifoot candles as poor, and below 3 millifoot candles as very poor. Of the 40 individuals tested by this method of classification, 16 were classed as good, 17 fair, 3 poor, and 4 very poor. There was an opportunity of rechecking 19 cases after taking vitamin A or carotene in oil. All showed an improvement as indicated by the test. The most spectacular improvement was shown in the poor and very poor cases who were given from 60,000 to 90,000 units of carotene in oil per day until they gave a response that might be classed good by the biophotometer test. These cases also improved clinically, and the amount of carotene in oil given was reduced to 30,000 units per day after the maximum improvement had been reached. While all these 19 cases improved, some seemed especially more responsive to carotene in oil. It was also observed that in the early months of pregnancy, most of the patients taking small doses of the vitamin A concentrate and having readings in the "fair" group, responded to larger doses of vitamin A concentrate and those re-checked improved their biophotometer tests to that classified as "good."

#### CASE HISTORIES

CASE 1.—(No. 104.) Mrs. J. F. P., white, aged 20 years, gravida ii. As a child, the patient ate irregularly and had frequent colds. From history it appears that the patient was more or less vitamin A deficient for the greater part of her childhood and markedly so during the years preceding this pregnancy. Patient was first pregnant at 16 years of age (1934) with an abortion due to accidental fall. There were no complications. In 1934 she had a tubal infection treated by the Elliot short wave; also an appendectomy and suspension of uterus in latter part of 1934; in 1935, pyelitis. Last menstruation, Dec. 14, 1936; delivered Sept. 25, 1937. On Feb. 5, 1937, she was admitted to the hospital with vomiting and hemorrhage; she continued to vomit until March 26, 1937, when she presented the following symptoms: Night-blindness; inability to stand even normal daylight (wore dark glasses and kept shades down); constant severe headache; constant vomiting—nothing tolerated; hair dry, coarse, and brittle; skin dry and scaly; eyes, cornea dull and lusterless; extreme weakness; and mild anemia.

Patient was referred for x-ray of sinuses with a negative report. The usual ophthalmologic examination revealed nothing to account for her symptoms. The patient was then referred for a biophotometer test. Her initial test on March 26, 1937 showed a low threshold and aptation test (Fig. 1). After three minutes' light exposure, 5.2 millifoot candles were required for her to detect the test spot.

Following the test the patient was given 60,000 units of carotene in oil for three days; then increasing to 90,000 units, decreasing the dose as improvement was shown on the biophotometer as given below:

#### BIOPHOTOMETER TESTS

March 26, 1937—5.2	millifoot candles of light
April 6, 1937—1.80	millifoot candles of light
April 26, 1937—0.52	millifoot candles of light
June 7, 1937—0.260	millifoot candles of light
July 10, 1937—0.380	millifoot candles of light
Oct. 6, 1937—0.69	millifoot candles of light after delivery



These two cases present the severe type of vitamin A deficiency, in which, unless prompt action had been taken the patients would probably have died and been classed as toxemia of pregnancy, and these illustrate the importance of the careful checking of all pregnancies for vitamin A deficiencies as early as possible.

Here we have two young women of the same age; both gave histories suggestive of prolonged vitamin A deficiencies; then with the beginning of pregnancy with the added nausea and vomiting, we find all conditions necessary to the production of a severe deficiency.

The second of these cases, as compared to the first, illustrated the importance of the continuation of an assured vitamin supply up to delivery.

#### SUMMARY

1. Severe deficiencies in vitamin A simulate so-called toxemias of pregnancy.

2. Women in the better class (financially) are often low in vitamin A during pregnancy, due to method of living and demands on their strength.

3. Administration of carotene in oil in severe deficiencies brought spectacular response.

4. Early check of all pregnancies with the biophotometer is important.

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Eichner, E.: Value of Knee-Chest Exercises in Postpartum Retrodisplacement, Ohio State M. J. 33: 1233, 1937.

The study comprised 316 women having 402 deliveries in the obstetric service at Mount Sinai Hospital; 22.7 per cent of the uteri of 211 patients instructed in knee-chest exercises during their stay at the hospital were found in a posterior position at their first dispensary examination, while 27.7 per cent of the uteri of the 191 patients not so instructed were retroplaced at their first post-partum examination. In the entire series 101 patients, or 25.1 per cent of the total, had retrodisplacements at their initial post-partum visit. The percentage of posterior displacements increased with the parity from 20 in the primiparas to 41.2 in the quintiparas; 30.4 per cent of the posterior displacements treated by knee-chest exercises were failures and, of these, 6 patients responded to the use of a pessary and 7 were discharged. In cases in which the pessary failed, the knee-chest position also failed. In twelve patients the uterus became anterior without treatment for the retrodisplacement in an interval less than that required for either pessaries or knee-chest exercises. The conclusion is that knee-chest exercises are valueless in the treatment of post-partum retrodisplacement except during the third and fourth weeks of the puerperium, when these exercises appear to reduce the percentage of displacements.

J. P. GREENHILL.

The patient was referred for biophotometric examination with the following results (Fig. 2):

May	10, 1937	—4.4 millifoot candles
June	20, 1937	—1.80 millifoot candles
August	1, 1937	—0.59 millifoot candles
Oct.	1, 1937	—2.40 millifoot candles after delivery

After the initial test, the patient was first given 60,000 units of carotene in oil, increasing to 90,000 for several days until improvement was shown on the biophotometer reading; then the amount was reduced. On Aug. 1, 1937, the patient was rechecked by the photometer with a high normal reading. She felt better than she had ever felt. At this time the patient, who was never very cooperative, stopped taking carotene and took no more before she was delivered Sept. 19, 1937.

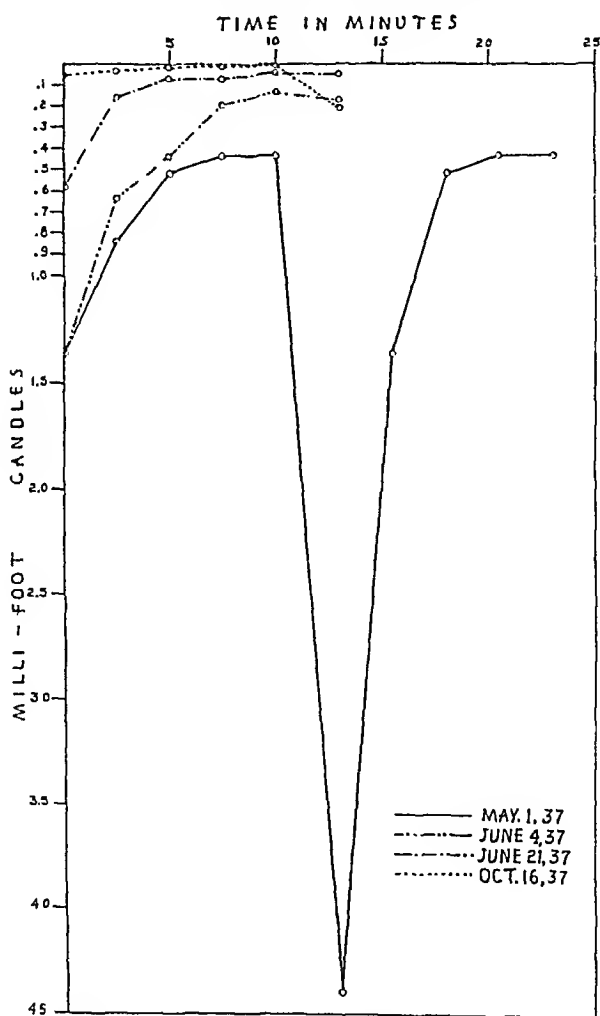


Fig. 3.—Biophotometer test curves on Case 2.

Following delivery, the patient was rechecked with the biophotometer and was again low. She presented the following symptoms at this time: Tiring easily, marked nervousness, weakness, and insufficient lactation.

Lack of cooperation on the part of this patient shows her in marked contrast to the other patient. She did not continue her vitamin regime long enough to supply a reserve. She in no way followed instructions.

2. The intramural stretching of the ureters in the bladder wall with stenosis. If the intramural stretching in the bladder wall were the primary reason, you would naturally expect the dilatation of the ureters to occur from that point. This has not always been shown.

3. Compression of the ureters outside the bladder. Concerning this theory, regarding the compression of the ureters outside the bladder, Brettauer and Rubin feel that if the bladder were a solid structure compression of the ureters as they were drawn through the pelvic outlet would be possible, but, since the bladder itself is compressible and not solid, they believe that the ureters could not be sufficiently compressed. However, it is an established fact that obstruction of the upper urinary tract can result from certain anatomical arrangements of blood vessels, as when there is an aberrant renal artery running to the lower pole of the kidney. Upon release of this obstruction, the dilatation of the upper ureter disappears. The anatomic relationship of the lower end of the ureter and the uterine artery shows that the ureter passes under the uterine artery to reach the bladder. As the uterus is prolapsed more and more through the pelvic outlet, the uterine arteries become slings over the ureters and, if this condition persists, the ureter becomes partially obstructed and the secondary changes above the obstruction progress. The changes of hydro-ureter followed by pyelitis and pyonephrosis and, finally, renal insufficiency are similar to the changes that occur in prostatic obstruction in the male, or, as a matter of fact, any lower urinary obstruction.

Together with the autopsy findings of Case 6, I am also reporting five additional cases of prolapse of the uterus and bladder in which x-rays showed urinary changes. In order to obtain the data regarding the urinary systems in these patients, the following procedures were used:

Besides a complete physical examination and a thorough history, a routine urinalysis was performed. Nonprotein nitrogen, creatinine, and sugar determinations were made on the blood. A phthalein function test was done on the kidneys. X-rays of the urinary tract were taken, using intravenous neo-iopax. The pyelograms were taken with the patient standing and also lying down. The same determinations were made after operation when the patient returned for check-up.

CASE 1.—Mrs. E. H. (Hospital No. 18308). This 54-year-old, white female entered the hospital complaining of something falling out of her. As far as she knew this had been going on for about four years. About three weeks before admission, while standing, the uterus prolapsed about four or five inches. Heretofore, it had only presented at the vulva. At the present time she is only nine years past the menopause, has had two children, and, according to her story, had no difficulty with her deliveries. General physical examination, other than the prolapse, revealed a blood pressure of 195/100. Urinalysis was entirely negative. Phenolsulphonephthalein test was 78 per cent in two hours; blood Wassermann test, negative; blood non-protein nitrogen, 39.2; blood sugar, 114.2 mg.; creatinine, 1.28. She was operated upon two days after admission. The Manchester type of vaginal repair was performed. She made a normal convalescence and was discharged in good condition.

CASE 2.—Mrs. S. H. (Hospital No. 15580). This 37-year-old woman stated that for the past year she had had "falling of the womb." She had been married eleven years and had three children. The first labor was very prolonged and delivery was by means of instruments. Her menstrual flow had been normal for the past four or five months. She had been unable to keep her uterus in the pelvis—it presenting outside the vulva at all times.

On physical examination there was nothing very abnormal except the prolapse of the uterus. Her urine on two occasions contained a slight amount of albumin. There were no casts. The blood pressure was 180/95; blood nonprotein nitrogen, 37.6 mg.; sugar, 94.7; creatinine, 1.24; phenolsulphonephthalein test, 50 per cent in two hours. Because of the marked ulceration of the prolapsed uterus and vagina, it was decided to hold the uterus temporarily in place by fixing it to the anterior abdominal wall. This was done under ether anesthesia. The patient was discharged to return for further repair.

## THE CHANGES OF THE URINARY TRACT ASSOCIATED WITH PROLAPSE OF THE UTERUS

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IN RECENT years numerous articles have been published regarding the surgical treatment of uterine prolapse. Most of these have stressed the advantages, techniques, and results of the various types of surgical procedures recommended by the individual authors. Vaginal hysterectomy, obliteration of the vagina, interposition of the uterine body, and, more recently, the Manchester type of parametrial fixation are operations of choice. The authors of these various articles have failed generally to stress the complications of neglected uterine prolapse. The changes that occur in the urinary tract in women who have suffered for a long time from prolapse of the uterus should be re-emphasized, particularly the obstruction of the lower urinary tract with resulting hydronephrosis, pyonephrosis, and renal insufficiency.

Three particular reasons have prompted the following investigation. First of all, the average patient, when asked why she did not have the prolapse repaired, occasionally replies that "she had received medical advice that the condition would never kill her and, if it did not interfere with her activities, to neglect it." The cases that I wish to report will show that this is an erroneous statement. Second, the post-mortem study of a woman who had had complete prolapse of the uterus for twenty years (Case 6) suggested that the bilateral pyoureters and pyonephrosis which were found had resulted from the slinglike structure of the uterine arteries as they were pulled over the ureters. Third, since surgery is being employed possibly more frequently than in the past, some justification for its continued practice seems necessary.

The obstruction of the urinary tract in procidentia is not a new observation. In 1846 Virchow described the changes in the urinary tract with marked prolapse of the uterus. Halban and Tandler expressed the opinion, from a study of their autopsy findings, that the dilatation of the ureters was due to the compression outside the bladder. Brettauer and Rubin reported that frequent secondary findings in cases of neglected prolapse of the bladder were pyoureter and pyonephrosis.

The three theories frequently offered for the mechanical obstruction of the passage of the urine from the kidneys through the ureters, bladder, and the urethra in cases of prolapse of the uterus are as follows:

1. Kinking of the urethra and stasis with cystocele. If the obstruction were primarily in the urethra with strangulation, you would expect frequently to find a large amount of residual urine. From our observation this is not true.

Efforts were renewed in the direction of forcing fluids by means of a continuous intravenous drip. Though her sensorium remained absolutely clear, she began to show signs of uremia with occasional twitchings and generalized shaking, not true convulsions. She continued to be nauseated constantly and to vomit at very frequent intervals. On the tenth day she had a very definite sudden convulsive seizure and died.

#### POST-MORTEM FINDINGS

*Gross Examination.*—The body was that of a fairly well-developed but thin elderly white woman, 151.25 cm. (60.5 inches) in length, and 66 years of age. Rigor mortis had not yet developed and there was only slight post-mortem lividity of the dependent portions. There was no edema of the face or extremities. The hair was gray and abundant. The ears and nasal passages were negative. The eyes were blue-gray, the pupils being round, equal and regular. The upper and lower teeth were replaced by false plates. The neck was thin. The chest was symmetrical. The breasts were small and grossly normal. The abdomen was flat and soft. There were venepuncture wounds and ecchymosis in both antecubital fossae. Just above the internal malleolus of the right ankle was a short incision 2 cm. in length through which intravenous glucose had been administered.

There was complete eversion of the vagina due to extreme prolapse of the uterus. The cervix of this organ presented at the most dependent portion and exhibited one large and several small superficial erosions. The entire mass was inflamed and exuded a foul odor.

*Peritoneal Cavity.*—The body was opened with the usual Y-shaped incision. The subcutaneous tissues were moderately moist. The omentum which was thin was stretched over the abdominal organs and was adherent to the abdominal walls just below the brim of the pelvis. On reflecting this, approximately 400 c.c. of turbid reddish yellow fluid were found free in the pelvic cavity and also about the various viscera. The serosal surface of the cecum was dark purplish red and covered with adhesions. In attempting to free the cecum and ascending colon, it was found that they formed part of a large adherent inflammatory mass which also included the right kidney and ureter and a considerable amount of perirenal fat. A similar large adherent mass was found on the left side of the abdomen. These will be described in more detail later.

In the pelvis only the fundus of the uterus was seen. It was present in a depression in the pelvic floor through which the body of the organ had prolapsed. The Fallopian tubes were stretched due to the tension of the prolapsed uterus.

*Adrenals.*—These glands were essentially negative.

*Kidneys.*—The entire genitourinary tract was removed en masse and then carefully dissected. Both kidneys were surrounded by a large amount of fat which, as it was removed, was seen to be infiltrated with a thin, reddish gray, foul-smelling, inflammatory fluid. As the fat immediately around the kidneys was removed the fluid became definitely purulent. Both organs were soft, large, and contained many thin-walled, fluctuant, cystic cavities. In stripping a piece of capsule from the surface of the left kidney, the underlying cortex was so thin and cystlike that the tissue ruptured and permitted considerable dark brown, foul-smelling, purulent material to escape.

Before continuing with the examination of the kidneys, a probe was inserted into the urethra and this structure was opened to the bladder. The bladder was contracted and did not contain any urine. Its wall was thickened. The mucosa was grayish brown and necrotic and was thrown into deep folds which were covered with the same sort of fluid purulent material that was contained in the left kidney.

Both ureters were markedly distended, thickened, and appeared dark purplish red in color. They were 2 cm. in diameter, and there was evidence of constriction in them about 3.5 cm. from the bladder where the uterine arteries cross, as shown in Fig. 1. On opening the left ureter at its entrance into the bladder a large amount of the same gray, foul-smelling, purulent fluid poured from it. The entire

CASE 3.—Mrs. L. W. (Hospital No. 22116). This 59-year-old housewife had had a sense of lack of support for the last two years, and for the last six weeks had complained of a tumor coming from the vagina. She also complained of burning and frequency of urination. There was no incontinence of urine. Blood pressure was 150/92. Urinalysis showed a trace of albumin and an occasional white blood cell. Examination of her blood showed a nonprotein nitrogen of 29 mg. per cent, creatinine 1.1 mg. per cent, sugar 100 mg. per cent.

After two weeks' hospitalization she was operated upon. A vaginal hysterectomy and posterior repair were performed under ether anesthesia. She was discharged three weeks after operation in good condition.

CASE 4.—Mrs. E. B. (Hospital No. 18645.) This 48-year-old patient stated that she had never been pregnant and, for the last twenty years, had had something protruding through the vagina. The condition progressed, until eight years ago when the patient could not keep the uterus inside her without wearing some type of support. For the past six months she had been unable to replace the uterus. She also complained of frequency of urination and constipation. Urinalysis was entirely negative. Blood pressure was 150/80. Because of the edema and ulceration of the prolapsed uterus, it was replaced and held in place by a Menge pessary, and the patient was advised to return home. At that time blood examination showed non-protein nitrogen 42.4, sugar 118.3, creatinine 1.4, phenolsulphonephthalein test 85 per cent in two hours. She returned about six weeks later. The pessary was removed and a vaginal hysterectomy was performed. Her convalescence was uneventful except for a cystitis which developed two weeks after operation. Catheter specimen of urine showed many pus cells, and *Streptococcus viridans* was isolated.

CASE 5.—Mrs. B. O. (Hospital No. 19013.) This 72-year-old woman, mother of five children, stated that the first sensation of bearing-down discomfort in her pelvis was observed twelve years ago. It did not bother her a great deal until two years ago when she fell down and injured her knee cap. When she got up and around after six weeks in bed, she noticed that something protruded from the vagina. This had become progressively worse until she sought consultation. Blood pressure 180/95. Urine showed many white blood cells, otherwise negative. Blood chemistry: nonprotein nitrogen 35.2, sugar 39.7, creatinine 1.2; phenolsulphonephthalein test 75 per cent in two hours.

After several days' preparation in the hospital, a Manchester type of operation was performed. Her convalescence was uneventful, and she was discharged in good condition.

CASE 6.—Mrs. I. G., aged 66 (Hospital No. 12299). For the past six years this woman had had a prolapse of the uterus, which produced no more symptoms than a dragging down feeling and general inconvenience. During this time she lost 81 pounds, but had continued to do her usual housework. For three weeks her bearing-down pain had been severe and she was prevailed upon by her friends to seek medical attention.

Thirty-three years ago her only pregnancy terminated in a difficult instrumental delivery of a stillborn child.

Physical examination was of a dehydrated emaciated woman, very alert. Except for moderate thickening of the peripheral blood vessels, the only other finding was a complete uterine prolapse. Her urine was strongly positive for albumin and the sediment showed many pus cells. She had a moderate secondary anemia and her white blood cells were elevated to 18,000. Blood sugar was 158.8 mg. per cent; blood nitrogen, 120 mg. per cent; creatinine was correspondingly elevated to 3.4 mg. per cent; and the chlorides were normal. Carbon dioxide combining power was 15.5.

The obvious dehydration was combated with intravenous glucose and subpectoral saline daily, so that by the third day her nonnitrogen had dropped to 109.6 mg. per cent and creatinine to 3.38 mg. per cent, and her carbon dioxide combining power rose to 26 per cent.

## CONCLUSIONS

1. In neglected cases of uterine prolapse, changes in the urinary tract may result.

2. These changes, hydroureter, hydronephrosis and, eventually, renal insufficiency, are probably caused by obstruction of the lower end of the ureter by the slinglike position of the uterine artery as it is pulled over the ureter.

3. Replacement of the uterus by pessary or operation relieves the obstruction.

4. Complete histories and laboratory findings in five cases of prolapse of the uterus and post-mortem findings in one other case are reported.

The author desires to thank Dr. John A. Sampson for advice and permission to include certain cases.

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## A STUDY OF A CAUSE OF HYDRAMNIOS

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ONE of the causes of hydramnios and of its commonly associated fetal lesions, is infection.

In 1931, Goodall published a paper entitled "Hydramnios, a Theory and a Discussion,"<sup>1</sup> in which it was advanced that hydramnios, in most cases, is the result of an infective inflammatory hypersecretion of the amnion, and that the defections in the fetus also depended upon that same agency. It was also pointed out that in cases of hydramnios one is always cautious as to the prognosis of the fetus, owing to the frequency of fetal defects. A study of these defects made it very clear that in cases of hydramnios, the fetal anomalies were always the same. They fell into distinct categories: (1) A normal child; (2) external deformities, such as synechias or amputations due to inflammatory adhesions or bands; (3) hydrocephaly; (4) spina bifida with meningocele; and (5) anencephaly. It was pointed out that the uniformity of these fetal defects associated with hydramnios, argued a common causal agency and that amnionitis answered the problems. Inflammation of the amniotic sac could account for the hypersecretion of fluid, for the synechiae, for the adhesions and amputations, and it was pointed out that the intensity of this inflammation would determine whether there would be merely hypersecretion, or whether there could also be fusions of contiguous parts and amputations of limbs. It was also argued that the result of amniotic infection upon the fetal nervous system would depend upon the time of the amniotic invasion in relation to the stage

length of the ureter was opened. The mucosa was considerably thickened, appeared to be focally neerotic and was soft and greenish gray.

The left kidney was then incised longitudinally. The pelvis was distended and filled with the same sort of material as found elsewhere. The parenchyma was almost entirely replaced by large and small cysts. In a few places there were remnants of cortical pyramids extending inward between the cysts.

The right kidney and ureter were not opened at this examination. Grossly they resembled in all respects the left organs and a museum specimen will be made from the entire genitourinary system to show one kidney and ureter intact while the other organs will disclose the deeper changes.

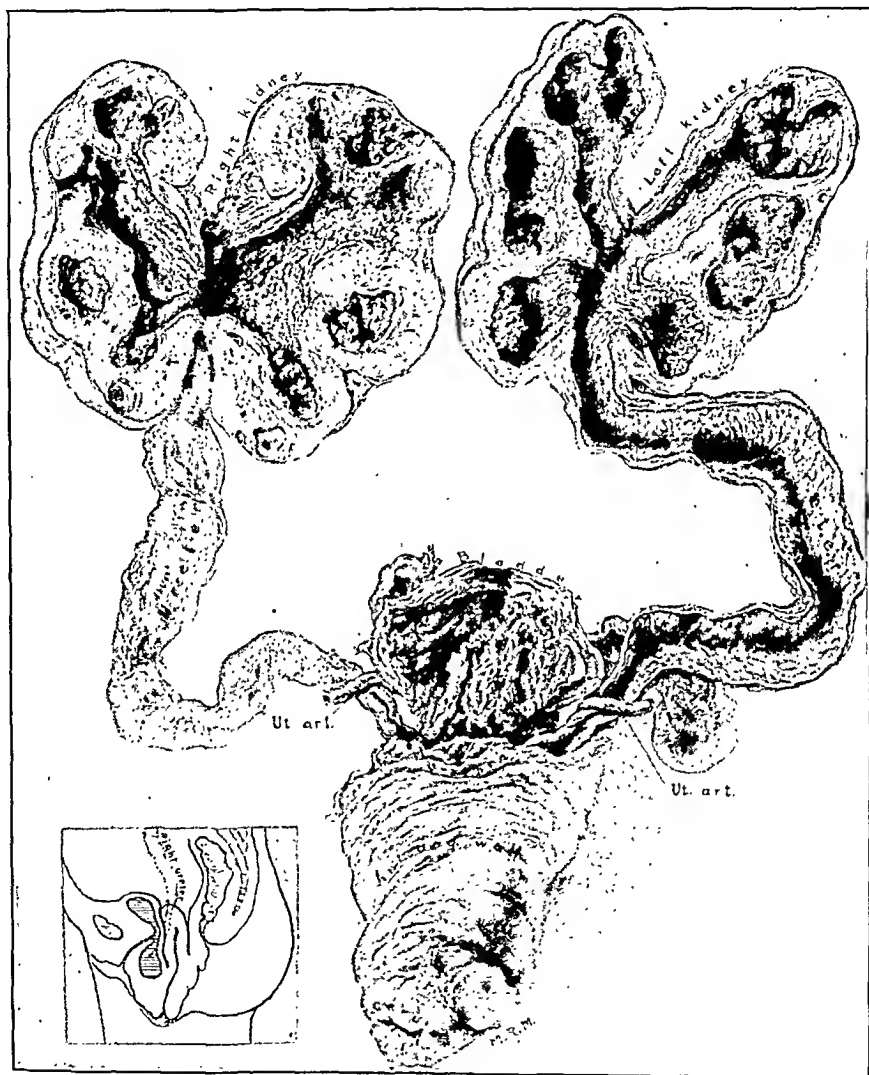


Fig. 1.

*Genitalia.*—The prolapsed uterus was small and atrophic. There was a small leiomyoma in the wall of the fundus. The Fallopian tubes and ovaries were also atrophic. The fimbriated extremity of the left tube was stretched over a parovarian cyst, measuring 3 by 2 cm. On the anterior surface of the everted vagina, there was a fairly large area of hyperkeratinization of the mucosa measuring 3 cm. in diameter. On the posterior surface there were several much smaller similar lesions.



nervous system of the child before closure of the neural canal, it might be possible to demonstrate infective processes in the other organs of the body, and most likely these would be found in the heart, the only organ operating at normal capacity at that time. Accordingly, a careful autopsy was performed. No gross lesions were found, except two pericardial milk spots on the posterior wall. Numerous blocks were taken from all the organs, and these were carefully mounted.

The sections of the cerebral ventricular lining showed signs of blocking of the lymph spaces by lymphocytes, and thrombosis of a few of the smaller blood vessels (Fig. 2). But in the heart there were all the signs of a well-defined infection of the adventitia at one side of the coronary arteries, and an infiltration of the contiguous muscularis of the artery in about one-fourth of its circumference, and internal to

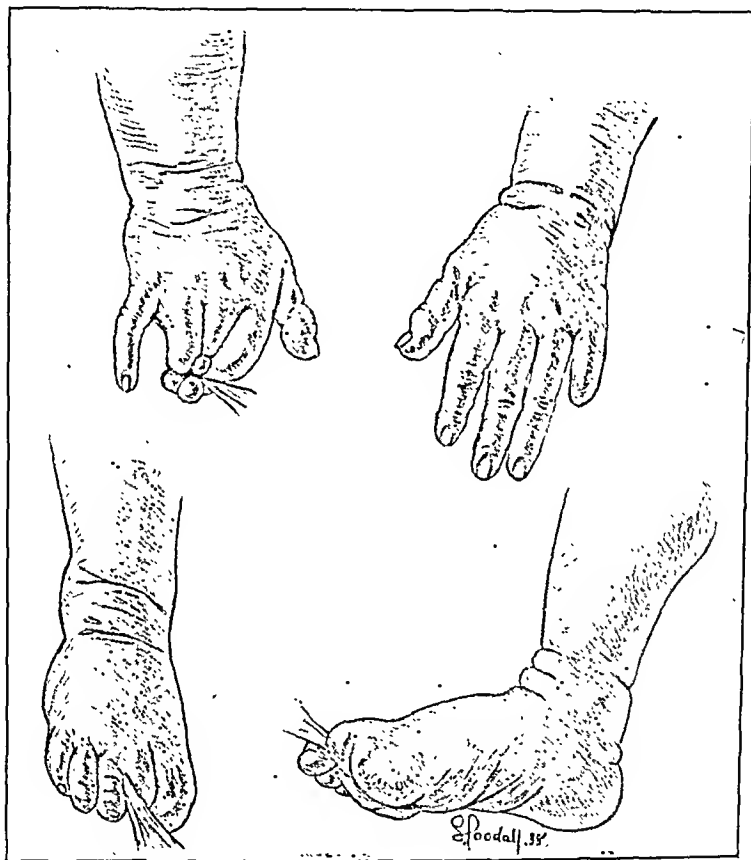


Fig. 1.—Showing amputated and deformed digits.

this, a clear-cut endarteritis, involving one-third of the arterial caliber, lifting the intima off its bed, but leaving the other two-thirds of the intima intact (Fig. 3). The dominant leucocytic infiltration was eosinophilic. There was thickening of the pericardium at two spots. The parent's Wassermanns were negative; there was no evidence of infection elsewhere. On questioning, the patient stated that she was seized with a subacute tenacious cold just about the time she became pregnant. It is thought that one or more of her sinuses were probably involved, judging from the tenacity of the infection.

The evidences point, therefore, to an infection of the amniotic sac, invasion of the spinal system and an occasional invasion of the fetal blood stream by an aberrant microbe, not a septicemia in the true sense, but the common temporary, possibly recurrent invasion. That the amniotic fluid and fetus do become infected from a primary focus in the mother is shown by the following case, reported now for the first time.

of fetal development. The neural canal of the fetus is developed from the fetal ectoderm, which is continuous with the amnion. So, if infection got into the amniotic sac after the fetal spinal cord had already closed, the child's nervous mechanism would not suffer, and external adhesions at that later date, when fetal movements had probably already developed, would be almost impossible. Therefore, in cases of late hydramnios, normal babies would be the rule. If, on the other hand, the amniotic infection developed just before the cord closed at its latest closing parts, that is, the cervical and lumbar regions, then spinal closure would be completed before hypersecretion of the brain ependyma and cord membranes had developed, and hydrocephaly would be expected to develop later. If, again, the amniotic infection developed at an earlier date, before the spinal closure, hypersecretion would set in, and internal spinal pressure would prevent closure and spina bifida would consequently develop. And last, if the amniotic infection got into the nervous system in the early stages of the neural development, normal growth would be inhibited and the consequence would be an anencephalic monster. It may be emphasized here that an examination of the fetus of abortions frequently reveals acute infective processes in the amnion, and exudate in the crevices of contiguous fetal parts. Such acute infections frequently associated with preabortal maternal fever invariably result in death of the fetus and a casting off of the products of conception. In the less acute cases, where the infection inclines more to the exudative than to the hypersecretive types, especially before fetal movements have begun, synechias and adhesions will be the dominant defects. Whereas, in the lowest types of infection, the common types, hyperfunction, that is, hydramnios, will be the dominant sign. These types of infection, when access to the fetal nervous and other systems is obtained, lead to changes variable in degree and extent. In the milder forms this condition may remain local in the ventricles of the fetal brain. In the more acute cases, the infection may spread by the blood stream to other systems.

That this explanation is probably correct is shown by the following cases:

CASE 1.—A primipara, 38 years of age, weight 88 pounds, 5 feet in height, consulted Goodall. She had a justomino pelvis, and it was decided to perform a cesarean section at full term if there was any disproportion. She was examined three weeks before full term. There was a definite, but mild, degree of hydramnios, and it was quite impossible to make out the presentation. An x-ray was taken, which showed a breech with an enormous hydrocephaly, which filled the whole sub-diaphragmatic area. A cesarean section was done, and after delivery of the body, the aftercoming head was so enormous that the posterior fontanel was punctured to facilitate extraction. Fully a quart of fluid escaped from the ventricles. Examination of the body revealed a fusion of three fingers which were nearly amputated by a tough thready adhesion which had an attachment to the amniotic wall, but which was broken on delivery, and a tag 2 inches long pendent from the constricted fingers. The little finger of the other hand had been cleanly amputated by an adhesion. Two toes of one foot were fused and almost amputated by a thready adhesion, and two toes of the other foot were cleanly amputated, the attachment of which outside the big toe was still plainly visible (Fig. 1). It was at once hypothecated that if an infection of this severity had caused these deformities and had entered the central

later, showed roughly 200 colonies. Acute hydramnios came on, and Goodall passed a small trocar through the anterior vaginal fornix, between the bladder in front and the lower uterine segment behind, for purposes of culturing the amniotic fluid. A large amount of fluid was allowed to escape slowly. After this had run some time, some of the fluid was collected as it escaped, for culture. The growth was a pure culture of the specific streptococcus. Two days later the membranes were ruptured and a living fetus was born, and cultures of its blood gave a pure growth of the same organism. The amniotic placental surface was then seared with the iron, and a small portion of placenta was cultured in medium, and gave a pure growth also. The baby died a few hours after birth. Autopsy was refused. Here we have direct evidence of invasion of the amniotic fluid, and of the fetal blood stream from the maternal cardiac focus.

## COMMENT

It is not contended that all cases of hydramnios are due to infection. We do know that other causes, such as cardiac decompensation with venous stasis, will produce hydramnios, as will also congenital fetal cardiac and renal diseases, but it does seem conclusive that maternal foci of infection can, and may, transmit that infection to the amniotic sac, and if early enough may infect the fetal neural system, and may produce infectious changes in other organs. What the above related cardiac infection would have meant in a viable child, whether coronary constriction or continued infective myocardial changes would supervene, are very debatable points. However, the matter is one for theorizing, for the hydrocephaly precluded any prolonged extrauterine life in this case.

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## CONCENTRATION OF SERUM SULFATE DURING PREGNANCY AND IN PRE-ECLAMPTIC TOXEMIA\*

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THERE is probably no other condition in which the borderline between health and disease is less sharply marked than it is in the toxemias of pregnancy. Apparently, only slight alterations in physiology are necessary to convert the condition of the normal pregnant woman into one of the varying degrees of illnesses incident to one of these toxemias. Chemical analyses of the blood of patients afflicted with the toxemias of pregnancy have been significant by the absence of changes which were uniformly of diagnostic or therapeutic value. Plass has demonstrated that the concentration of the nonprotein nitrogen of such patients is within normal limits. The concentration of uric acid in the blood of the pre-eclamptic patient is increased. When the pregnant

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CASE 2.—A secondipara was seen by Goodall in consultation with a cardiologist. The patient had mitral stenosis with decompensation. She was then two and one-half months pregnant. Therapeutic abortion was recommended. The advice was not heeded. At the seventh month, the patient developed an acute infective endocarditis, implanted upon the chronic. High fever and chills developed. The first blood culture showed 50 colonies of *Streptococcus viridans*. A second culture, ten days

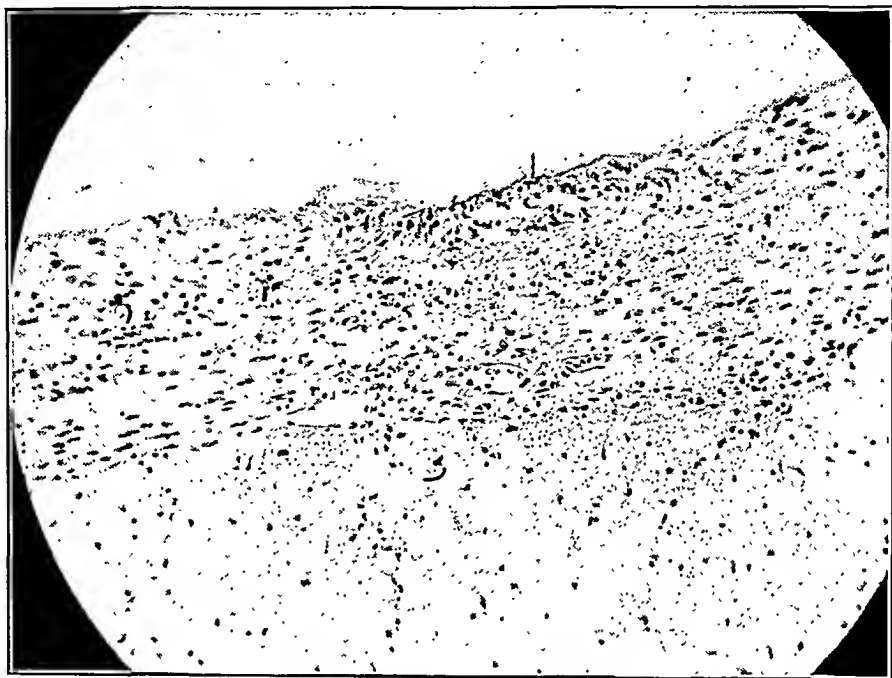


Fig. 2.—1, Ventricular lining; 2, thrombosed vessels; and 3, medulla.



Fig. 3.—1, Cardiac muscle; 2, extravascular inflammation; 3, subintimal exudate; 4, coronary artery; and 5, elastica.

ously observed by one of us had a concentration of serum greater than 5 mg. of sulfate (1.3 mg. of sulfur) per 100 c.c. of serum. Fig. 1 shows the results of serial serum sulfate determinations made during normal pregnancies. In 16 of the 55 cases the value for sulfates was elevated 5.0 mg. per 100 c.c. of serum or more, one day post partum. In the first 39 cases represented in this table, the concentration of serum sulfate was within normal limits both at the time of delivery and again on about the ninth day post partum, with the exception of Case 37. The table shows a most interesting finding in the association of the symptoms of pre-eclamptic toxemia and the concentration of serum sulfate. Often, as indicated in the same table, in Cases 39, 40, 41, 42, 44, 45, 46, 48, 49, 53, and 54, representing those patients who had exhibited symptoms of pre-eclamptic toxemia, the concentration of serum sulfate was in the upper range of the normal or it was increased. In fact, 12 of 18 patients whose serum disclosed an abnormal increase in concentration of sulfate during

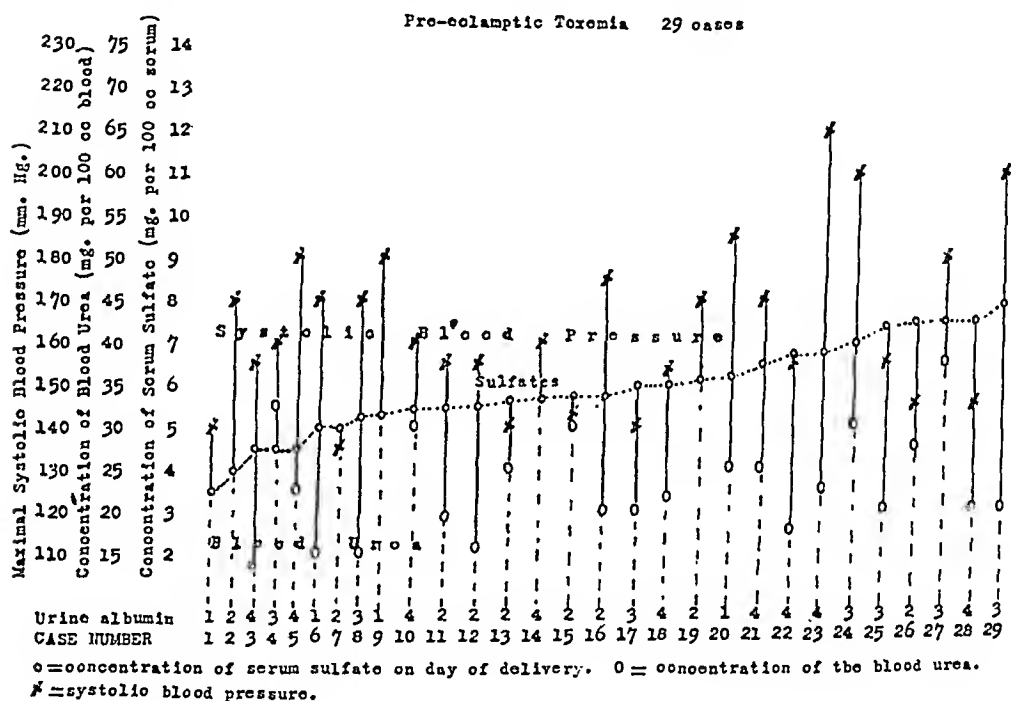


Fig. 2.—Graphic representation of the concentration of serum sulfate, the concentration of blood urea, and the systolic blood pressure at time of delivery of 29 women who suffered from pre-eclamptic toxemia.

pregnancy experienced pre-eclampsia, while none of those whose serum gave consistently normal values for sulfate throughout pregnancy suffered from toxemia. The increase in serum sulfate values antedated the appearance of toxemia in nearly all cases. However, in Cases 43, 47, 50, 51, 52, and 55 the concentration of serum sulfate was increased but the patients did not have symptoms of pre-eclampsia.

In Fig. 2, the concentration of serum sulfate, the concentration of blood urea and the systolic blood pressure at the time of delivery in 29 cases of pre-eclamptic toxemia are shown. This figure, for practical purposes, is a duplication of Fig. 1. Patients represented by Cases 1 to 7 inclusive had normal concentrations of serum sulfate although they displayed symptoms of pre-eclamptic toxemia. Patients represented by Cases 8 to 29 inclusive had both an increased concentration of serum sulfate and definite pre-eclampsia.

We have observed the concentration of sulfate to be definitely increased in the serum of 6 patients who had eclampsia. In association with the toxemias of pregnancy incident to an impaired renal function,

woman becomes edematous, there may be an increase in the concentration of plasma chlorides and a decreased concentration of the plasma proteins. In the presence of severe toxemia (eclampsia), the patient may be dehydrated and thus present a hyperazotemia.

The object of this study was to determine the concentration of serum sulfate both during normal gestation and at the time symptoms of pre-eclamptic toxemia and eclampsia developed.

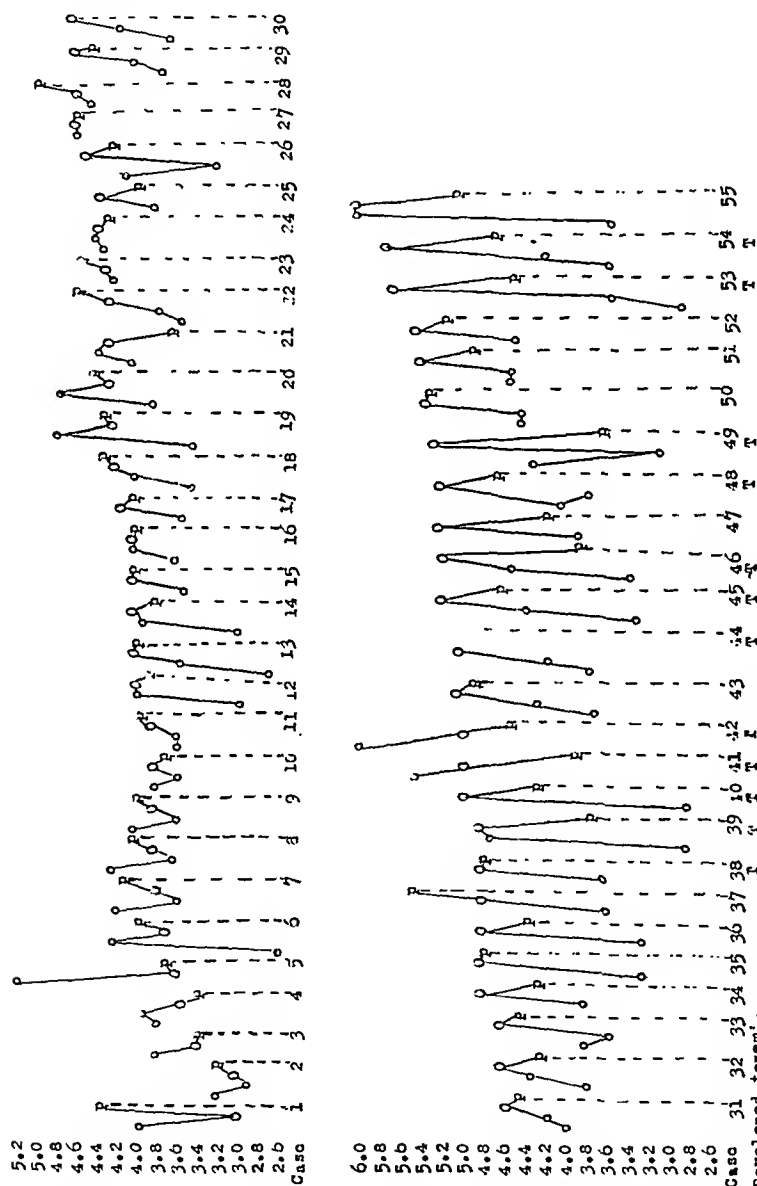


Fig. 1.—Graphic representation of the results of serial serum sulfate determinations made during the normal pregnancies of 55 women.

As shown in Fig. 1, the study was conducted according to a single plan. During the first trimester of pregnancy, if the patient appeared to be within the limits of the normal, if the urinalysis disclosed no abnormalities and if the blood pressure was within normal limits, the concentration of serum sulfate was less than 5 mg. of sulfate (1.6 mg. of sulfur) per each 100 c.c. of serum, a normal range of concentration of this substance. Less than 2 per cent of 125 nonpregnant individuals previ-

# CONCOMITANT RUPTURED ECTOPIC PREGNANCY, HYDROPS OF THE GALL BLADDER, AND OVARIAN CYST

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A SURVEY of the literature reveals a case in which ruptured ectopic pregnancy was associated with acute cholecystitis (Eisenklam) and one case in which ruptured ectopic pregnancy was associated with chronic cholecystitis and cholelithiasis (McKay). Numerous cases have been reported in which unilateral ovarian cysts were present in ruptured ectopic pregnancy and an occasional case of this condition combined with bilateral ovarian cysts has been described. The combination noted in the title of this paper has not been previously recorded.

The patient was a 24-year-old white woman who was admitted to the West Baltimore General Hospital, June 15, 1938, complaining of pain in the right lower quadrant of three days' duration. The last regular menstrual period began thirteen days prior to admission and lasted for six days. The patient began to bleed slightly from the vagina six days before coming to the hospital. This bleeding had gradually increased and had been profuse for two days. Three days before admission, dull steady pain began in the right lower quadrant and became progressively worse. On the day she entered the hospital, the pain became much more severe and the appetite was impaired. She did not vomit or feel nauseated. There was no right upper quadrant pain. The patient explained that she "was menstruating fifteen days too early."

The gastrointestinal history revealed that there had been pain in the epigastrium for a year which came on about an hour after meals and was relieved by self-induced emesis. The patient had had frequent belching, but no "spells of vomiting" had occurred. There had been no pain under the "shoulder blade," jaundice, constipation, abnormal stools or hemorrhoids. Cardiorespiratory history showed some shortness of breath during her second pregnancy. Genitourinary history brought out the fact that the patient had had a nocturia for six months. Menstruation began at the age of 16. The periods occurred every twenty-eight days and lasted for six days. She was married seven years ago and has two children, both in good health. There have been no other pregnancies.

The patient was a well-developed and nourished woman of stated age, who was lying quietly in bed in no acute pain. The temperature was 100° F., the pulse 100, and the respirations 22. The blood pressure was 135/88. She was in unusually good spirits. Abdominal examination revealed doubtful right upper quadrant rigidity. A mass was present in the gall bladder region which extended from 6 to 7 cm. below the right costal margin downward about 8 cm. toward the umbilicus. At this point the mass, which was 4 cm. in cross diameter, was lost in the border of the right rectus muscle. On pelvic examination, a mass about the size of a lemon was felt in the right adnexal region. A doubtful fullness was felt in the left adnexal region.

Laboratory examinations disclosed a negative urine and an erythrocyte count of 5,100,000. A leucocytosis of 12,000 with 72 per cent polymorphonuclear cells was present. The blood Wassermann was negative. On the day following admission, the leucocyte count was 11,000 with 68 per cent polymorphonuclear cells and the blood sedimentation rate was 15 mm. (Wintrobe method after correction).

The patient was observed for three days and during this time she complained of moderate right lower quadrant pain. Her temperature and pulse were normal and her morale was good. The preoperative diagnosis was chronic pelvic inflammatory disease.

On June 18, operation was performed under second nitrous oxide and ether anesthesia. A lower midline incision was made and the exposed peritoneum was

such as glomerulonephritis, the concentration of serum sulfate may be either increased or normal, according to the status of the renal functional activity.

#### COMMENT

The sulfate of the serum is derived mainly from the metabolism of protein. It has been our experience that the concentration of serum sulfate is usually increased when renal insufficiency is present. It is, oddly, true that in some cases of renal sufficiency (about 10 per cent), concentration of sulfate may be increased until it is more than that which is present in the serum of a normal individual before there is an increase in the concentration of blood urea. Yet, if patients are dehydrated, as they often are in the presence of pyloric obstruction and obstruction of the urinary tract, the concentration of blood urea may be increased, while the concentration of serum sulfate remains within normal limits.

The increase in the concentration of serum sulfate in the presence of pre-eclamptic toxemias and eclampsia is a curious phenomenon. We do not believe that the increased concentration of serum sulfate plays any part in the production of, but is rather an effect of, these toxemias. Our data are not sufficient to permit formation of conclusions. Our experience, however, gained in extensive studies of the concentration of serum sulfates in both health and disease, leads us to believe that many patients having pre-eclamptic toxemia and eclampsia also have some impairment of the renal function.

If the increase in concentration of uric acid in the toxemias of pregnancy is due to hepatic faults, as Cadden and Stander have suggested, it may be that the increased concentration of inorganic serum sulfate also is related in some way to an impaired hepatic function, since the conjugation of sulfates is probably a function of the liver

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- (1) *Cadden, J. F., and Stander, H. J.*: AM. J. OBST. & GYN. 37: 37, 1939.

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Gernez, L., and Omez, Y.: *Twin Pregnancy Considered from the Point of View of Prognosis and Conduct of Labor*, Rev. franç de gynéc. et d'obst. 37: 916, 1938.

Twin pregnancy occurs once in 84 labor cases and two-thirds of them are found in multiparas. Rarely does a twin pregnancy go to full term. Most of them terminate in the eighth month. Abortion occurs in about 10 per cent. The most frequent complications of twin pregnancy are albuminuria, hydramnios, and eclampsia. Generally the second twin gives more trouble during delivery than the first. Spontaneous delivery took place in only 53 per cent of the cases of this series. The maternal death rate was 1.3 per cent and the fetal mortality was 18.5 per cent for the first twin and 23 per cent for the second twin. The prognosis of twins depends upon the degree of prematurity and the operative interventions.

The maternal and fetal prognosis was improved when both babies were delivered within less than fifteen minutes.

J. P. GREENHILL.



The symptoms and signs of the present case are atypical of all three conditions found at operation. The case well illustrates the degree of pathology which may be present and still produce few symptoms. It also brings out the confusing picture which ectopic pregnancy may present even after rupture has taken place. The clinical picture of this condition is very frequently not characteristic.

## A PHENOMENAL SINGLE OVUM TWIN PREGNANCY

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THIS case of a single ovum twin pregnancy presents features which, from a clinical and pathologic standpoint, are interesting and puzzling. We propose, therefore, to record both aspects of the case in some detail.

### CASE REPORT

H. T., a white, 19-year-old primigravida, entered the St. Louis Maternity Hospital on Nov. 7, 1937, in active labor. From her menstrual history she was six weeks from term. She received her prenatal care at a municipal clinic and was diagnosed a twin pregnancy, which was confirmed by x-ray examination. The patient had not been to the clinic for over a month. She stated she had suffered severe headaches and had noticed some edema of the extremities during the week previous to admittance. At the time of entry to the hospital, she showed pitting edema of the ankles, but there were no other significant physical findings. The blood pressure was 130/80. Urinalysis revealed a two-plus albumin, but was otherwise negative. The pelvic measurements were normal. The patient was hastily admitted to the delivery room, since the head was visible at the vulva. Twenty minutes later the first baby was born spontaneously, following a right mediolateral episiotomy. The second baby, a full breech presentation, was also born spontaneously five minutes afterward. The third stage of labor lasted five minutes. The puerperium was uncomplicated and the patient was discharged from the hospital on the tenth post-partum day.

The first of the single ovum twins to be delivered was a macerated male still-born, weighing 2,360 gm. The other twin was then delivered without difficulty. The cry and respirations were spontaneous. The infant was quite plethoric; the skin presented a deep bluish red color over the extremities and face, and an intense hyperemia over the trunk. Immediately following birth, the temperature dropped to 35.7° C., and moderate respiratory difficulty was noted. These symptoms rapidly disappeared with routine CO<sub>2</sub> and O<sub>2</sub> inhalations and elevation of body temperature. However, the color of the skin was unchanged. The only pathologic findings, aside from the abnormal color of the skin, were a slightly enlarged spleen and liver. The birth weight was 2,100 gm., the occipital frontal circumference was 32 cm. and the length 44 cm. After the first two days, the infant became quite active, taking its feedings eagerly and doing unusually well without the customary routine premature care required for newborns of this birth weight. There was no evidence of intracranial, pulmonary or cardiac abnormality. The Kline and Wassermann tests on mother and baby were negative.

On Nov. 9, 1937, the second day of life, because of persistent hyperemia of the skin, a red blood cell count was done and found to be 8.2 million. The following day, the red blood cells had dropped to 7.68 million. The hemoglobin was 18.0 gm. (Sahli). The white blood cell count was 2,500, stabs 3, segments 21, lymphocytes 76; all apparently normal cells. No erythroblasts were seen. The platelets appeared to be markedly reduced. The bleeding time was normal (two minutes).

seen to have a bluish color. When this was opened, about 250 c.c. of liquid and clotted blood was found in the pelvis. A large clot was present about the fimbriated end of the right tube, and when this was removed a point of rupture was seen about one inch from the opening (Fig. 1). The left tube was thickened and slightly injected and an ovarian cyst about the size and shape of a small orange was present. A bilateral salpingectomy and a left oophorectomy were done. The blood in the peritoneal cavity was evacuated. The appendix was removed. Routine palpation of the gall bladder at this time showed it to be greatly enlarged so that it extended to the region of the umbilicus. The primary incision was closed and an upper right rectus incision was made. One hundred cubic centimeters of white bile was evacuated from the gall bladder by paracentesis and a stone about the size and

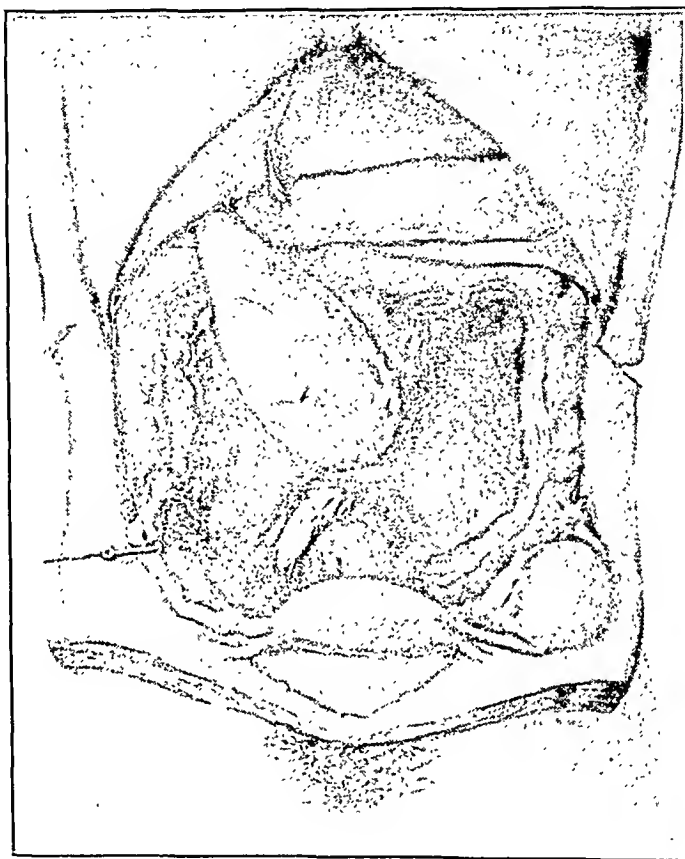


Fig. 1.

shape of a robin's egg was palpated in the cystic duct. The gall bladder was removed from below upward. A cigarette drain was placed in the foramen of Winslow. A smooth convalescence occurred and the patient left the hospital on the sixteenth postoperative day. She has been followed for about six months. Since leaving the hospital it has been possible for her to do her own housework. She had slight epigastric pain on one occasion, but this was relieved by taking cascara. Cascara is taken about once a week for constipation. There has been no emesis and her belching has been much less pronounced. No indigestion with "fatty foods" has been experienced. The patient did not menstruate the first month following the operation. Her period was three days late the second month and they have been regular since that time. She has had occasional twinges of the lower abdominal pain.

The pathologic report was hydrops of the gall bladder with acute cholecystitis, ruptured ectopic pregnancy, ovarian cystoma, chronic salpingitis, and chronic appendicitis.

absence of pulmonary, cardiac, or umbilical cord abnormalities was against a circulatory disturbance as a cause of the plethorism. The possible exogenous causes which might result in a defective oxygenation of the blood were ruled out.

The presence of other findings suggests that the abnormal increase in red blood cells originated within the fetal tissues. These findings are: leucopenia, thrombocytopenia, marked prolongation of the clotting time, thick gelatinous blood, with a relative or actual decrease in serum content, and unusual changes in the placenta.

The placenta showed many interesting and unusual findings. In the first place as stated above, it was a single ovum twin placenta. Due to pathologic changes arising in the fetal blood vascular systems, there was a sharp line of demarcation between the two portions of the placenta supplying the fetuses. It is well known that the fetal vessels grow down through the umbilical cord and unite with those from the placenta which arise *in situ* in the villi. It is, therefore, easy to see that the chorionic villi destined to become the chorion frondosum are divided between the two fetuses, but it is unusual to find these portions so clearly defined.

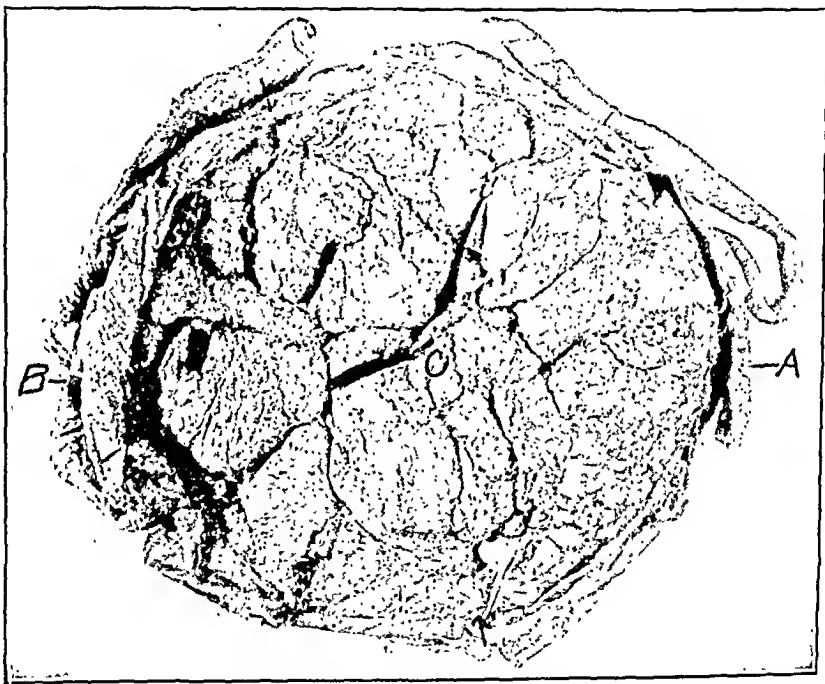


Fig. 1.—A indicates the ischemic portion of the placenta which nourished the macerated stillborn fetus. B designates the deep purplish red portion of the placenta which nourished the living infant.

Not so easily explained are the gross picture of ischemia; the microscopic picture of avascularity, hydropic degeneration of many of the villi and the persistence of Langhans' cells up to thirty-four weeks' gestation in the placenta of the macerated fetus (Figs. 1, A and 3). As indicated above a similar but more profound blood dyscrasia may have existed which caused the fetus to perish, and the placental pathology may be secondary to fetal death. We have seen repeatedly this picture in placentas, which have been retained in utero after the death of the fetus from any cause. The viability of the chorionic tissue is dependent on maternal and not on fetal circulation, as exemplified in cases of early villi before fetal vessels have formed and in cases of hydatidiform mole, where there is an absence of fetal vessels, yet there is marked proliferation of the trophoblast. The prolonged viability of the placental tissue is thus explained. The fetal circulation stopped with the death of the fetus, and the vessels became obliterated. Therefore the placenta had an anemic appearance. There was no evidence of white infarction. Of course, it

The clotting time was definitely prolonged (twenty-four hours plus). At no time were there any hemorrhagic manifestations.

On the fourth day, 20 c.c. of blood were removed for study. On the following day another 20 c.c. were removed, for the possible benefit of combatting the polycythemia by lowering the blood volume. From the first sample, only sufficient serum could be recovered to perform the Kline test. The second sample of blood was centrifuged for five hours at high speed, but no serum was obtained. The blood was unusually thick and gelatinous in consistency. At no time was the infant dehydrated; however, daily subcutaneous injections of lactate-Ringer's solution were given, in an effort to dilute the blood. By the seventh day of life, the red blood cell count had fallen to 6.56 million and the skin had lost its bluish red color, appearing only moderately hyperemic. The platelet count was 32,600. On the following day, the red blood cell count was 6.2 million, the white blood cell count was 10,000 and differential: juveniles 2, stabs 23, segments 15, lymphocytes 58, monocytes 2, and reticulocytes 3.0 per cent. The clotting time had dropped to twenty minutes. The urine showed a trace of albumin, but no cells. At one month of age, the red blood cells had fallen to 5.76 million. The platelets rose to 576,000, the white blood cell count was 12,100 with a normal differential. Clotting time was ten minutes and bleeding time three minutes. The skin had returned to its natural color. X-rays of the long bones showed no abnormality. The infant was discharged on Dec. 15, 1937, weighing 3,100 gm., a gain of one kilogram in thirty-eight days.

When the patient was again seen, at the age of three months, the red blood cell count was 5.0 million. The spleen was not palpable, and the infant's growth and development were normal for its age.

Grossly, the placenta was that of a twin pregnancy, measuring 26 by 21 by 2 cm., and weighing 1,150 gm. The fetal surfaces were smooth and glistening. Both cords were eccentrically attached, the one from the viable baby being edematous. The septum between the fetuses was composed of two layers of amnion. The maternal surface showed a sharp line of demarcation between the placental tissue supplying the fetuses. Fig. 1, *A* shows the portion of the placenta which nourished the macerated stillborn, having an ischemic appearance, but otherwise normal. Fig. 1, *B* shows the portion of the placenta supplying the viable infant having a deep purplish red color, the gross picture of red infarction.

A section through the junction of the red and gray areas, Fig. 1, *C*, shows a very unusual microscopic picture (Fig. 2), which is described in the legend. Fig. 3 is a high power photomicrograph of the area of placenta attached to the dead fetus, labeled *A*, Fig. 1, and shows hydropic degeneration and avascularity of many of the villi. Other villi show poor vascularization. Some of the villi are still covered by both trophoblastic layers, Langhans' and syncytial cells, even though the pregnancy is of thirty-four weeks' duration. The part of the placenta described as *B*, Fig. 1, nourishing the viable infant, shows the fetal vessels markedly distended with blood and in many areas the vessel walls have ruptured and the blood has extravasated into the stroma of the villi, being confined only by the syncytial covering. The villi are closely crowded with inadequate intervillous spaces. Fig. 4 shows a high power photomicrograph of this area. A section through the septum between the fetuses, which is composed of two amniotic membranes, corroborates the gross diagnosis of a single ovum twin pregnancy.

#### DISCUSSION

The blood changes which occurred in the living infant are difficult to explain satisfactorily. It is suggestive that similar, but more pronounced blood changes were present in the macerated twin, which, indeed, may have accounted for its death, but unfortunately a post-mortem examination was refused. The polycythemia cannot be explained on the basis of anhydremia, in view of the absence of dehydration and lack of concentration of other blood elements.

It is probable that the abnormal hyperemia of the skin and mucous membranes was secondary to engorgement of the capillaries with erythrocytes, since the skin became normal in color when the red blood cells dropped within normal range. The

is possible that some other cause may have existed to produce the death of the fetus, and the same picture would be present.

Ordinarily Langhans' cells disappear from the villi from eighteen to twenty weeks. We have never seen them persist so long a time as this. Their function is not known, but it is thought they have something to do with metabolism, since they disappear after the placenta is well developed. Perhaps the baby died before the usual time for these cells to disappear (eighteen to twenty weeks) and there was no further development of this portion of the placenta. However, the weight of the baby (2,360 gm.) would indicate that it was viable for a much longer time.

The gross picture of marked congestion and the microscopie picture of red infarction in the portion of the placenta nourishing the viable fetus (Figs. 1, B and 4) is not actually red infarction. Placental infarction is produced by cutting off the maternal circulation, either arterial or venous. Because of this interference the trophoblast is injured by the lack of oxygenation and by a collection of noxious metabolic products from the fetus. As a result of the damage to the epithelium of the villi, there is a response to tissue injury on the part of the capillaries of the villi. The vessels of the villi are turgid with blood and at times become dilated to



Fig. 4.—A high power photomicrograph of an area of the placenta supplying the living infant. The fetal vessels are markedly engorged and have ruptured in places so that the blood is confined by the syncytial covering. The villi are closely crowded with comparatively little intervillous spaces.

the point of rupture. In this case the whole of that portion of the placenta supplying the viable infant showed this change, and it would be incompatible with the life of the fetus if it were red infarction. We, therefore, sought another explanation of this pathologic picture. We believe the picture in the placenta is secondary to the unexplained, temporary polycythemia in the fetus. The fetal circulation was so engorged from the increase in blood volume that the vessels of the villi were markedly dilated and in many instances the pressure was so great that the vessels could not withstand it and rupture occurred with extravasation of blood into the stroma of the villi. The maternal circulation was intact so that nourishment could be carried to the fetus and excrementitious materials removed.

#### SUMMARY

A single ovum twin pregnancy is reported showing the following salient points:

1. One twin was a macerated, male stillborn, weighing 2,360 gm.
2. The other twin weighed 2,100 gm. The infant was quite plethoric and the skin was a bluish red color. The baby was found to have polycythemia. The red blood cell count was 8,200,000. The white blood cell count was 2,500. The platelets were reduced to 32,600. The bleeding time was normal. The clotting time was defi-

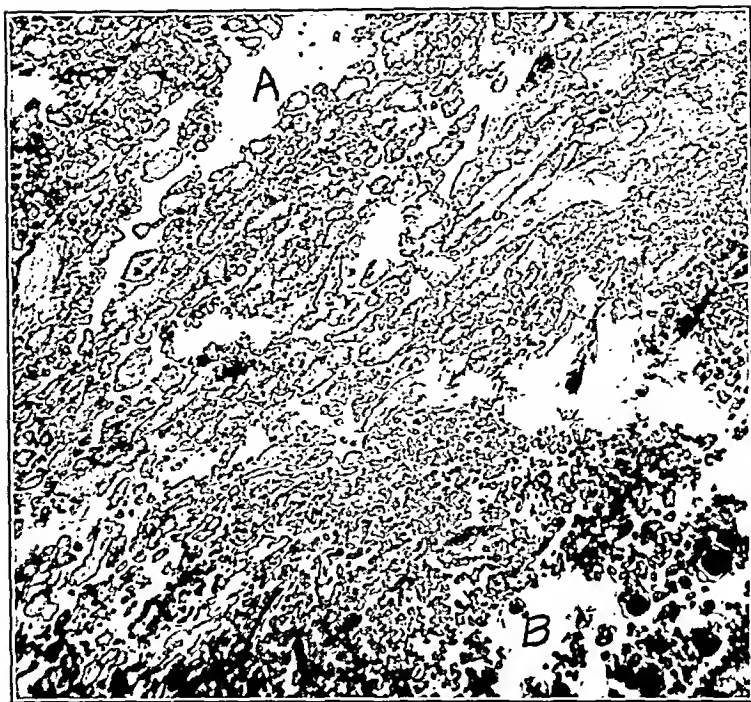


Fig. 2.—This is a low power photomicrograph of an area at the junction of the two portions of the placenta, designated *C*, in Fig. 1. *A*, represents the portion attached to the stillborn, and shows large hydropic villi and *B*, defines the part of the placenta supplying the living infant and clearly pictures marked congestion of the vessels of the villi.



Fig. 3.—A high power photomicrograph of the area of the placenta attached to the stillborn fetus. Note the hydropic villi, some avascular, others poorly vascularized. In some villi both trophoblastic layers are distinguishable.

majus and minus, just below the level of the clitoris. She had been aware of the nodule since she was in her teens. However, it did not start to grow until the month previous to excision. When it was excised on Sept. 19, 1938, it was the size of a pea, soft in consistency, freely movable and not painful or tender. A pre-operative diagnosis of hidradenoma of the vulva was made.

*Histologic Examination* (Fig. 1).—The intact squamous epithelium lay just above the tumor. There was a thin, but definite connective tissue capsule with a few scattered sweat glands in the periphery. The lesion itself was composed of papillomatous proliferations within a cyst. The proliferations branched and gave the tumor the appearance of a labyrinth in some areas. There was a thin connective tissue core to the proliferations which were lined by a single layer of cuboidal or columnar epithelium. The cell boundaries were not definite, but the nuclei were clear, large, oval, or round in shape, and basically situated. The epithelium also formed acini which were of varying size and shape. A few of the acini were distended with secretion and had a flattened epithelium; others were lined by a double layer of cells, an inner columnar or cuboidal, and an outer flat or spindle layer. There were a few groups of cells in the connective tissue stroma which resembled those of the lining epithelium, but which showed no evidence of gland formation. However, there was no impression of malignancy.



Fig. 1.—Case 1. The tumor is situated in the corium beneath the intact squamous epithelium and consists of papillary proliferations within a cyst.

CASE 2.—Mrs. E. K., aged 55 years, gravida iv and para iii, entered the hospital on Aug. 23, 1937, because of diabetes, hypertension, and a right inguinal hernia. She had had a vaginal hysterectomy for a fibroid uterus on Sept. 16, 1925. The lesion on the vulva was found during a routine examination. The nodule was located in the midline of the fourchette, being about 0.5 cm. in diameter. It was fixed to the vaginal mucosa and appeared to have a very shallow ulceration. A senile vaginitis and kraurosis and leucoplakia of the vulva were also present. The inguinal glands were palpable and firm. A biopsy was performed on Aug. 5, 1937, and a wide excision on Aug. 24, 1937.

*Histologic Examination.*—This tumor lay just beneath the squamous epithelium and was composed of papillary proliferations and acini similar to those described in Case 1. It had a lobulated appearance with distinct evidence of intraeystic proliferation in only one of the lobules. There was no definite connective tissue capsule, but the lesion was well demarcated without evidence of malignancy. In one area the epithelium was composed of large, pale, cylindrical cells closely resembling those of the apocrine and mammary glands. At the periphery of the tumor, there were areas of round cell and plasma cell infiltration and a few sweat glands.

nately prolonged. The red blood cell count gradually dropped until it was 5,760,000, at the end of the first month of life. The platelet count mounted to 576,000 at the same period of time. The baby was discharged thirty-eight days after birth, weighing 3,100 gm. and in apparent good health. At three months of age, the child was perfectly normal for his age.

3. The placenta was that of a single ovum twin pregnancy. The portion that had supplied the stillborn infant was grayish white in color and that nourishing the viable infant was bluish red in color, a startling contrast in the division of the placental tissue between the fetuses. We believe the pathologic changes in the portion of the placenta which had nourished the stillborn are secondary to the death of the fetus. It is suggested that the fetus may have died from a blood dyscrasia, similar to that of the viable twin. The unusual congestion in the placenta nourishing the living infant was considered to be secondary to temporary changes in the hematopoietic system of the baby.

## HIDRADENOMA OF THE VULVA\*

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**D**URING the past ten years, we have seen five cases of hidradenoma of the vulva at the Jewish Hospital of St. Louis. In view of the fact that these cases are comparatively rare, about 40 in the literature with only 2 case reports from America,<sup>1, 2</sup> and as there is some question of the potential malignancy of this tumor, we felt that it was worth while to describe our cases and summarize the findings of others. Our cases are of further interest in that they seem to present various stages in the development of the tumor.

Werth, in 1878,<sup>3</sup> and Schickele,<sup>4</sup> in 1902, reported cases which undoubtedly were hidradenomas of the vulva; both assumed that the tumor arose from aberrant epithelium. Werth mentioned no specific anlage while Schickele believed that they arose from remnants of Wolffian ducts because of the resemblance to kidney, testicle, and Wolffian structures in general. Landsteiner<sup>5</sup> and others contended that these tumors may represent aberrant mammary tissue. Braun,<sup>6</sup> in 1892, was the first to call attention to the possibility of formation of adenoma of the sweat glands of the vulva. It remained for Pick,<sup>7</sup> in 1904, to point out the true nature of these tumors. He believed that they were in all probability congenital in origin and derived from malformed sweat gland anlage. He based his ideas on the resemblance of the morphologic traits of the hidradenomas to those of the normal sweat glands which consisted especially of the double-layered character of the epithelium and the presence of a membrana propria elastica around the tubules of the adenoma. Pick classified the adenomas of the sweat gland as hidradenoma tubulare, which are derived from mature sweat glands; hidradenoid adenoma, which are derived from epidermis or rudimentary sweat glands; and a combined form. The histologic structure of both the hidradenoma tubulare and the hidradenoid adenoma is similar, the difference being in that the former contains a sudoriferous duct which would tend to show that it arose from a fully formed sweat gland, whereas the latter is lacking in such proof. We believe, as do Landsteiner and Outerbridge, that Pick's classification complicates matters and that the single term "hidradenoma" should be used.

### CASE REPORTS

**CASE 1.**—Mrs. E. W., aged 48 years, gravida i and para i, was seen on Sept. 17, 1938. The patient had noticed a small nodule in the furrow between the right labium

\*This work aided by the David May-Florence G. May Fund.



age. The distribution of the cases according to the age at which operation was performed is as follows:

AGE GROUP	NO. OF CASES
25 to 29	1
30 to 39	8
40 to 49	16
50 to 59	5
60 -----	1

A few of the patients gave the history of having noticed the tumor for some time before its removal. This was true in Case 1, the patient having noticed the nodule when she was still in her teens, but the lesion did not grow until one month before its removal, at the age of 46. Gross<sup>8</sup> reported a case in which the tumor was present in childhood and was removed at the age of 43, after it had been increasing in size over a period of one year. Of the few case reports that mentioned the duration of the tumor, the time intervals between observance and removal were: 2 years, 2 years, 6 months, 3 months, and 2 months. Frequently the tumors were discovered by the physician during the course of an examination.

The hidradenomas occur more frequently on the labium majus, as 32 tumors were found in this location with only 12 tumors reported elsewhere on the vulva. Seven of the latter were located on the labium minus; 3 were situated between the labium majus and minus; and the remaining 2 were found on the posterior commissure. There may be more than one lesion in the same patient. Cases of 3 and 4 nodules in one patient have been reported by Pick and Gross, respectively.

The lesion is usually about the size of a pea, slightly elevated, and round or oval in shape. However, the size may vary considerably, ranging from 3 mm. in diameter (Woringer<sup>9</sup>) to that of a walnut (Schroeder<sup>10</sup>). Blau<sup>11</sup> reports one case in which pregnancy did not influence the size of the tumor. In 5 cases (Pick, Hoeck,<sup>12</sup> Schiffman,<sup>13</sup> Koehler,<sup>14</sup> and our case (5) the lesion was a polyp or funguslike growth. In 5 cases, including 2 of the present series, the surface was ulcerated. In 2 of these, bleeding was produced on touch. The tumor may be covered with hair and in a few cases has been described as red or pink in color.

The hidradenomas may be either firm or cystic. Three cases of Eichenberg's and 1 of Schroeder's were markedly distended with fluid. In such cases the papillomatous proliferation fill only a part of the lumen, whereas, in others it fills the lumen completely, giving the tumor a firmer consistency. In no case was the tumor tender, painful, or adherent to the underlying structures. However, in 3 cases it was described as adherent to the skin.

Histologically, hidradenomas may take the form of cystic nodules in which the lumen of the cyst may be partially or entirely filled with papillomatous proliferations. Papillary proliferations are the usual picture; they may take origin from a broad base or from a single pedicle. In all of our own cases, the origin was apparently from a broad base. The tumor may have a labyrinthine or papillomatous appearance or both.

The acini vary in form, shape, and size. Some are dilated and contain an amorphous secretion. The epithelium is usually a single layer of tall columnar cells on a well-marked basement membrane. Each cell contains a vesicular nucleus situated near the base. The epithelium may also be cuboidal or consist of a double layer of cells. The inner layer consists of columnar cells and the outer layer of flat spindle or cuboidal cells. In one of the 13 cases reported by Eichenberg the epithelium was double-layered throughout. He was also the first to describe collections of cells which resembled those of the apocrine and mammary glands. This is understandable from the probable common embryologic origin of the mammary and sweat glands. He found these cells in 5 of 13 cases and we have found them in 2 of our series. In addition to acinar formation, there are usually present masses and columns of epithelial cells embedded in the stroma without lumen formation. This feature has caused some authors to believe that the hidradenomas are potentially or definitely malignant. We feel that some of these collections of cells, at any rate, may be tangential sections through the edge of acini.

CASE 3.—Mrs. B. D., aged 45 years, gravida iii and para iii, entered the hospital on Jan. 24, 1934, for excision of a tumor that had been discovered accidentally on the left labium majus. It was about the size of a pea. The surface was ulcerated with well-defined margins. The tumor was solid on cut section.

*Histologic Examination.*—The squamous epithelium was ulcerated; the base and wall of the ulcer consisted of the well-circumscribed tumor mass. A very thin layer of concentric connective tissue fibers and a few areas of mild plasmocytic infiltration were present about the periphery. A ball of hyalinized connective tissue was located near the center of the tumor. There were areas in which the acini were lined by a double layer of epithelium and areas in which there were strands of epithelial cells in the stroma. Otherwise the tumor was similar in appearance to those described above.

CASE 4.—Mrs. A. J. R., a private patient of Dr. J. H. Armstrong, aged 58 years, was seen on June 11, 1934, with the history of having noticed a swelling of six months' duration on the right labium minus. It was about the size of a pecan. The tumor was excised on June 18, 1934. In January, 1937, this patient had a radical operation for cancer of the breast.

*Histologic Examination.*—This lesion showed areas of cyst wall which were composed of fibrous tissue lined by a flattened epithelium. The proliferations, however, protruded beyond the level of the squamous epithelium. The tumor was otherwise as described in the previous cases and here, too, there are small areas of cells resembling those of the mammary glands.

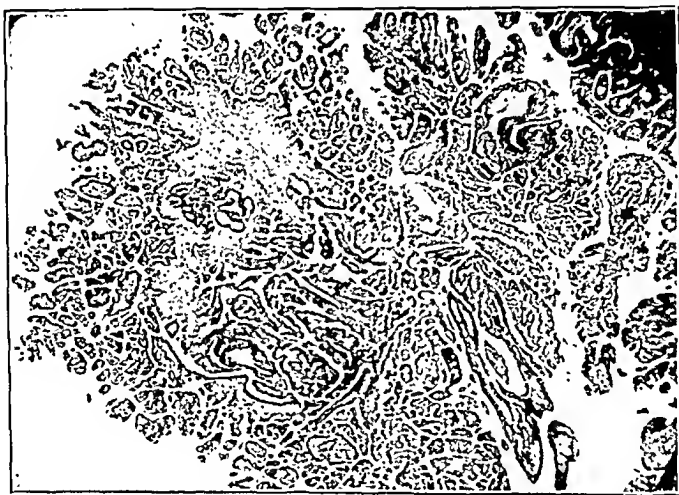


Fig. 2.—Case 5. The tumor consists of a polypoid growth with a marked increase in the connective tissue.

CASE 5.—Mrs. I. S., a patient of Dr. J. Orenstein, aged 49 years, gravida iii and para iii, was seen on May 5, 1936, with the history that during the past year she had noticed a small tumor on the left labium majus which would bleed occasionally. Examination revealed a pedunculated tumor about the size of a pea which was ulcerated and bled on touch. The tumor was excised on May 5, 1936.

*Histologic Examination* (Fig. 2).—Sections through the pedunculated tumor showed a polypoid growth lined by the same type of epithelium described in the above cases, with areas of a double layer of cells. The stroma, however, showed a marked increase in the amount of connective tissue over those previously described. No capsule was present.

In reviewing 37 cases in the literature, plus the 5 cases of our present series, the following information has been obtained.

Most of the patients have come to operation when they were in their fifth decade; the youngest, however, was 25 years of age and the oldest was 62 years of

## TREATMENT

Wide local excision of the lesion has been the usual method of treatment. In only 2 cases, both of which were suspected of malignant tendencies, was a more radical operation performed. One case was that of Eichenberg's in which an excision of the entire labium majus and an inguinal gland dissection of the corresponding side was performed. The other case was reported by Schwarz, who did a secondary excision of the labium.

## CONCLUSIONS

Five cases of hidradenoma have been presented and 37 cases from the literature have been reviewed. We do not believe that this tumor is as rare as the number of cases in the literature would seem to indicate, but rather that in many instances these small tumors have been overlooked. Hidradenomas of the vulva are benign.

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## NEPHRECTOMY DURING PREGNANCY\*

## IN A PATIENT WITH PRE-EXISTING HYPERTENSIVE DISEASE

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THE following report of a removal of the left kidney early in pregnancy has several unique features.

*History.*—The patient was a 31-year-old Jewish woman, married eight years, and pregnant for the first time. Her medical history had been uneventful until four years ago, at which time she had developed a toxic exophthalmic goiter. Her basal metabolic rate at the time was plus 80 per cent, and her blood pressure, though not elevated above the normal range, showed some widening of the pulse pressure. The treatment of her toxic goiter had been carried out at the University Hospital over the intervening four-year period, and had consisted of three operations upon the thyroid gland and a course of x-ray therapy. During this time her toxic symptoms had subsided, but she had gradually developed a marked and fixed arterial hypertension.

At the time of her first obstetric examination she was eight-weeks pregnant. Blood pressure was 190, over 130, and her pulse rate was 100. There were no obvious

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The connective tissue supporting structure is usually scant and delicate, but may be markedly increased in amount as is illustrated in comparing the sections of Cases 1 and 5 (Figs. 1 and 2). Occasionally there are areas of dense acellular connective tissue as is demonstrated in Case 4. Eichenberg and Hoeck report cases with similar connective tissue changes. The connective tissue may form septa and give the tumor a lobulated appearance. The connective tissue capsule shows a marked variation. It is completely absent in some cases, and in others varies from an incomplete capsule of concentrically arranged fibers to one which is thicker and completely encircles the tumor. The lining epithelium of the cyst wall resembles that of the acini of the tumor proper and may be found to vary from a double layer of cells to a single layer of flattened cells. There may or may not be a round cell and plasma cell infiltration about the lesion. In some cases, sweat glands, many of which are distended, are found about the periphery.

We believe that the hidradenoma starts as a soft, cystic tumor with a small papillomatous growth arising from a portion of the cyst wall (Case 1). As the tumor grows, it fills up the entire lumen of the cyst, giving it a firmer consistency. With continued growth the tumor mass pushes its way toward the plane of least resistance which is beneath the squamous epithelium. The pressure against the skin results in an ulceration of the squamous epithelium, with the base and wall of the ulcer formed by the tumor. This stage is illustrated by Case 3. Finally, the growth rises above the epithelium, forming a funguslike or polyplike tumor, as is found in Cases 4 and 5. We do not believe that this continued growth eventually leads to malignancy, but rather that the tumors which are malignant show this tendency from the start. This belief is supported by the fact that in the one case which was definitely malignant, the tumor consisted of a papilloma within a cyst rather than a funguslike growth.

Early investigators pointed out that there was a close resemblance between hidradenomas and malignant adenomas. As a matter of fact, Pick at first took them to be metastases of such growths. Schickele, who reported one of the first cases, considered the tumor malignant. However, it has since been rather definitely demonstrated that hidradenomas of the vulva are usually benign.

Of all the cases in the literature, only one, that of Eichenberg's, was definitely shown to have metastasized. This woman was 35 years of age. She developed a movable almond-shaped, cystic nodule on the left labium majus. Within the cyst was a papilloma. Microscopically this tumor showed a double layered epithelium with areas of marked epithelial proliferation and projection of strands into the surrounding tissue. The left labium was completely removed with the lymph nodes of the left inguinal region. In one small lymph node in the labium, metastasis was found. There were no recurrences of the tumor after two years.

Ruge<sup>16</sup> considered his tumor as definitely malignant, but both Burg<sup>17</sup> and Hoeck,<sup>12</sup> who reviewed his case, do not agree with him. Schwarz called his tumor an adenoma hidradenoides tubulare destruens because it showed destructive tendencies. In comparing his case with that of Ruge's, Schwarz believed that in the latter the evidence of invasiveness was less convincing than in his own. The other suspicious case was reported by Schiffman<sup>13</sup> in which there were no signs of penetration or of definite destructive tendencies, but the author believed that the irregularly arranged collections of polygonal cells within the tumor proper might be looked upon as a beginning carcinomatous degeneration. Outerbridge had considered his case as distinctly suspicious, but after more careful study was convinced that it was entirely benign.

In a follow-up of the 5 cases in our series, none were found to have evidence of a recurrence or metastasis after periods of 5 years, 4 years and 6 months, 2 years and 8 months, 1 year and 5 months, and 6 months. Outerbridge and Williamson<sup>18</sup> report no recurrence in their cases after 1 and 3 years, respectively. Woringer reported the only case of recurrence. The tumor was removed two years after the initial excision. Therefore, with the exception of the 1 definitely malignant case, and the 2 very doubtful ones, all hidradenomas of the vulva reported in the literature have had a benign course.

which is so often manifested when pregnancy complicates chronic hypertensive syndromes does not accelerate the underlying vascular or renal disease. On the other hand, there are no studies of the life history of such disease which evaluate satisfactorily the influence upon it of factors other than pregnancy, and which might be used as controls in attempting to appraise more precisely the deleterious effects of pregnancy alone. Such studies are greatly needed for comparison with the pertinent studies of Stander and Peckham<sup>5</sup> and of Corwin and Herrick<sup>6</sup> relating to pregnancy in hypertensive disease.

### SUMMARY

A case of hypernephroma of the left kidney complicating pregnancy is reported. Its unique features are as follows: (1) The existence of a benign nephrosclerosis with fixed arterial hypertension prior to the pregnancy and the discovery of the tumor. (2) Removal of the tumor and affected kidney in the sixteenth week of pregnancy, without effect upon the hypertension. (3) Successful maintenance of the pregnancy beyond the period of viability, and the delivery of a child which has survived. (4) Absence of evidence of acceleration in the patient's renal vascular disease twenty-one months following the childbirth.

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## OVARIAN PREGNANCY

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THE occurrence of ovarian pregnancy was generally conceded until Velpeau, in 1835, questioned the authenticity of cases that had been reported as such. In 1878, Spiegelberg laid down definite requirements, which must be met before such a diagnosis can be justified. These are, (1) that the tube on the affected side be intact, (2) that the fetal sac occupy the position of the ovary, (3) that it must be connected with the uterus by the ovarian ligament and (4) that definite ovarian tissue must be found in its wall.

Since Thompson's case, in 1902, there has been an increasing number of true ovarian pregnancies described, but at the same time, the comparative rarity of its occurrence is recognized. Remembering that rupture of the sac at an early period may occur, or that degenerative changes may occur at an early period without rupture, it is probable that a goodly number are not recognized as such.

### CASE REPORT

R. C., aged 27 years, para i, was admitted Oct. 25, 1937, complaining of pain in the lower left quadrant of the abdomen, of one month's duration, had had similar pain in 1932, which caused her to remain in bed for two weeks. Menses were regular and normal. Last period began Oct. 16, 1937, five days and no pain. She had a normal spontaneous labor, at term, in 1928.

*Physical Examination*: Chest normal, blood pressure 118/70, abdominal palpation showed tenderness over left pelvic area, vaginal outlet was parous, cervix was hypertrophied with widened and reddened external os. The fundus was anteriorly placed and mobile, but slightly enlarged and irregular in outline. Moderate-sized

residual phenomena referable to her thyroid gland except exophthalmos. At this time it was discovered that she had a large firm tumor occupying the left side of the abdomen, apparently fixed beneath the left costal margin and extending downward to the level of the left anterior superior spine of the ilium. Radiologic and urographic studies showed that the tumor involved the left kidney. Renal function studies indicated that excretory function was normal in the opposite kidney. The tentative diagnosis of the tumor was hypernephroma. Because the patient desired that everything possible be done to preserve her pregnancy, it was decided that surgical removal of the tumor should be attempted without preoperative irradiation.

A left nephrectomy was successfully performed in the sixteenth week of pregnancy by Dr. Alexander Randall through a left lumbar incision. The tumor and affected kidney measured 31 by 22 by 17 cm. Histologic examination confirmed the diagnosis of hypernephroma.

After an uneventful recovery from her operation the patient was examined at frequent intervals during the remainder of her pregnancy, which continued to the thirty-fifth week. She was admitted to the hospital on three occasions during this time for periodic checkup of renal function, and for the control of her hypertension, which gradually became more elevated as the pregnancy advanced. It was felt advisable to terminate her pregnancy, because in addition to gradually mounting blood pressure, and a significant rise in the blood urea nitrogen, a moderate albuminuria (0.8 gm. per 24 hours) had appeared by the thirty-third week. Renal concentrating function was normal.

Pregnancy was terminated in the thirty-fifth week by an elective cesarean section under local anesthesia. A premature (2,130 gm.) living infant was obtained. The mother's postoperative course was uneventful, and the threatening signs of renal decompensation which had developed just before delivery rapidly disappeared. Mother and infant left the hospital in good condition.

The patient's arterial hypertension has remained fixed in the twenty-one-month period since her delivery. She has shown no impairment of renal function. During the same period there has been no demonstrable recurrence or metastasis of the hypernephroma.

#### COMMENT

The combination of hypernephroma and pregnancy is rare. Equally rare is the opportunity for observing the effect of pregnancy upon an established hypertensive disease in a patient deprived of one kidney. Interest was centered upon this second aspect of the above case, because of the potential importance of the lessons to be derived therefrom.

The studies of Matthews<sup>1</sup> and of Prather and Crabtree<sup>2</sup> have shown that in nephrectomized pregnant women, the essential problem is the behavior of the remaining kidney in the third trimester of gestation. Although the majority of 365 such pregnancies studied by Prather and Crabtree progressed normally, a significant number of patients developed renal complications. Three women died in uremia, and one in eclampsia.

The data of Prather and Crabtree, however, are based upon cases in which the blood pressure was presumably normal at the beginning of pregnancy. Information concerning two nephrectomized pregnant women in whom there had been a pre-existent arterial hypertension is recorded by Henriksen and Spence<sup>3</sup> and by Melick.<sup>4</sup> One of these patients developed eclampsia, while the other went through her pregnancy uneventfully.

The fixed hypertension in our case was ascribed to a benign nephrosclerosis. The height of the prepregnancy blood pressure was formidable enough to have warranted caution in permitting pregnancy to continue even in a patient possessing both kidneys. The outcome of the case, however, demonstrates that pregnancy may occasionally be carried to the period of viability in this disease in spite of the removal of one kidney.

The absence of demonstrable impairment of renal function two years after delivery in a case like this furnishes no clue to the cost of the pregnancy in terms of permanent kidney damage. It would be difficult to believe that the renal stress

was extruded through the wall of the mass. The right pelvis contained a simple cyst of the ovary, 5.5 by 5 cm. The fundus showed several small myomatous nodules. A supravaginal hysterectomy and bilateral salpingo-oophorectomy was done.

*Pathologic Report.*—(Hosp. Case 81,333, Specimen No. 14,129.) (a) Uterus 65 by 60 by 49 mm. (supracervical hysterectomy), containing several small fibroids, the largest one being 18 mm. in diameter. Endometrium congested, uterine cavity of normal size. (b) Right tube 55 by 11 mm. with the distal end obliterated. (c) Left tube 59 by 12 mm. (d) Left ovary 85 by 65 by 50 mm. consisting of a more or less uniform mass, intensely hemorrhagic and grossly necrotic. The mass was surrounded by a thin walled capsule containing occasional compressed follicle cysts. (e) Right ovary, cystic, consisting of one simple serous cyst, 55 by 50 by 45 mm. (f) Moderately macerated fetus, 5.5 cm. long.

*Histopathologic Diagnosis.*—(a) Multiple, small fibroleiomyomas without degenerative changes. Moderately hemorrhagic endometrium in follicular phase. Several small fibroleiomyomas were present, without evidence of degeneration. The endometrium showed occasional areas of hemorrhage, all of them placed very superficially. The glandular pattern was of follicular type. (b & c) Chronic salpingitis. There was a mild diffuse fibrosis involving the tube wall and mucosa, the stroma of the latter being moderately thickened. Focal accumulations of lymphoid cells were found throughout mucosa and musculature. (d) Ruptured ovarian pregnancy. The left ovary consisted of a small shell of ovarian cortex containing occasional compressed, distorted follicle cysts, partly filled with old blood. The rest of the ovarian mass consisted of old blood clots and necrotic placental tissue, the latter being almost completely autolyzed. (e) Simple serous ovarian cyst. The ovary was occupied by a simple serous cyst (small), the wall of which consisted of fibrous connective tissue with occasional small retention cysts. The lining of the cyst was smooth, the cells being of the benign type. (f) Fetus. No sections were made through the fetus as it was deemed desirable to save specimen intact.

The pathologic examinations were made by Dr. Tomás Cajigas, M.D., Pathologist, Columbia Hospital for Women, Washington, D. C.

#### SUMMARY

An unusual case of ectopic pregnancy, without history or symptoms indicative of pregnancy.

Arrest of development and retention of fetus in sac.

Specimen conforms to requirements of Spiegelberg, plus recovery of fetus in situ.

## CARCINOMA OF THE CERVIX IN A GIRL OF NINETEEN YEARS

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THE extreme rarity of carcinoma of the cervix in the young has been shown in previous publications by Bonner<sup>1</sup> in 1927, Morse<sup>2</sup> in 1930, and Baldwin<sup>3</sup> in 1931. The last case report was published in 1936 by Ludwig<sup>4</sup> who quotes the statistics of the previous authors, covering a period of forty-eight years. They found only 6 authentic cases of patients with cervical carcinoma between the ages of 16 months and 14 years, and 7 patients between the ages of 16 and 20 years. Ludwig's case and the case reported here make a total of 9 patients with carcinoma of the cervix between the ages of 16 and 20 reported in the literature over a period of more than 50 years.

#### CASE REPORT

A colored female, married, aged 19 years, was admitted to the Brooklyn Cancer Institute on Oct. 10, 1932 complaining of vaginal bleeding and pain in the left lower abdomen, and the loss of 25 pounds in one year.

masses were felt in both adnexal regions and both were tender. The urine was normal. Hg 75, red blood count 3,850,000, white blood count 6,600.

At operation, Oct. 27, 1937, the mass, 6.5 by 6 cm., in the left pelvis was found to be immobile and covered by omentum, which was firmly attached. This was liberated and when attempt was made to free and mobilize the mass a fetus 5.5 cm.

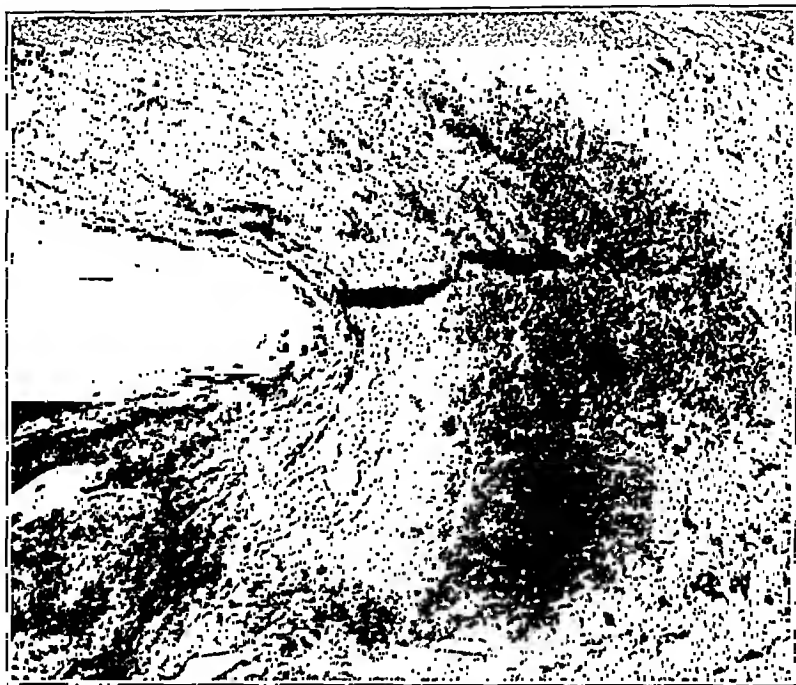


Fig. 1.—Ovarian cortex (magnification 80 diameters) showing follicle cyst and hemorrhage throughout stroma. Section was taken through most normal looking portion of ovarian tissue surrounding placental tissue.



Fig. 2.—Placental tissue and blood clots (magnification 80 diameters), showing numerous necrotic placental villi embedded in blood clots.



and lacerations of the hand. Her mother was dead, her father living and well. There was no history of cancer in the family. Her husband was infected with acute gonorrhea at the time of her admission.

Examination revealed a chronically ill, undernourished colored female, weighing 95 pounds, and appearing several years younger than her actual age of 19. Her temperature was 98.2° F., pulse 100, respiration 20, and blood pressure 114/82.

The abdomen was slightly distended, a large firm fixed tumor filled the entire pelvis and extended as far as the umbilicus. Vaginal examination revealed the entire parametrium and cervix fused into one hard, stony mass, continuous with the tumor palpated abdominally. The cervix and parametrium were covered with an ulcerating, sloughing malignant tissue, which could be wiped away with a sponge forceps. The rest of the physical examination did not show anything of note.

The blood Wassermann was four-plus. The blood count was 2,600,000 red cells, 50 per cent hemoglobin, and 18,500 white count. A biopsy from the cervix was reported as anaplastic carcinoma (Figs. 1 and 2).

The patient received x-ray therapy to the pelvis, but became progressively worse. The abdomen became distended with fluid, and she developed edema of the lower extremities. On Jan. 17, 1933, she was transferred to an institution for incurable cancer patients, where she died a week later. Consent for autopsy was not obtained.

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### SPECIFIC URETHRITIS IN A MALE NEWBORN

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(From St. Luke's Hospital)

**G**ENITAL gonorrhea is a relatively common infection among young children. However, it is extremely rare in the newborn. In fact, I have been unable to discover an instance of gonorrheal urethritis in the male newborn in the available literature. Villen gives an account of six cases of gonorrhea of the genital tract in newborn infants observed in material consisting of 16 boys and 31 girls, born of 47 mothers afflicted with gonorrhea. Of these, 6 girls had a vulvovaginitis with demonstrable gonococci. It is probable that the condition is occasionally overlooked. One author states that the symptoms are not uniform, and their intensity is extremely variable. In some cases the redness, swelling, and discharge are insignificant. In others there are considerable demonstrable findings. The mode of infection is not unanimously agreed upon. Some writers feel that infection occurs later while others admit an intrapartum infection. One might certainly think that breech presentations and premature rupture of the bag of waters with subsequent infection of the amniotic cavity predispose to infection. Hence, because of its rarity, the following case report is submitted.

G. M. C. (Hospital No. 52103) was born to a white primipara, 23 years of age, on Aug. 16, 1938. The mother reported for antepartum care on March 18, 1938. History at that time disclosed no evidence of previous specific infection. Examination revealed a healthy woman who was five months pregnant. Kolmer and Kahn tests were negative. Vaginal smears were negative for gonorrhea. Pelvic measurements were within normal limits. Subsequent antepartum course was uncomplicated. The delivery was spontaneous after a 19-hour labor (second stage 2 hours). Perineum was intact. The baby was a normal male, weighing 8 pounds 2½ ounces. One per cent silver nitrate was instilled in the eyes. The puerperium was afebrile. On the

The patient was a nullipara. She began to menstruate at the age of 13. Her periods were always regular and lasted three days. Her last normal period was two years previous to admission. Since then she had developed menorrhagia, metrorrhagia, foul leucorrhea and dysparunia. For thirteen days before admission she had bled quite profusely.

Her past history was inconsequential. She had suffered from "rheumatism" for a number of years, had been in an automobile accident, receiving some abrasions

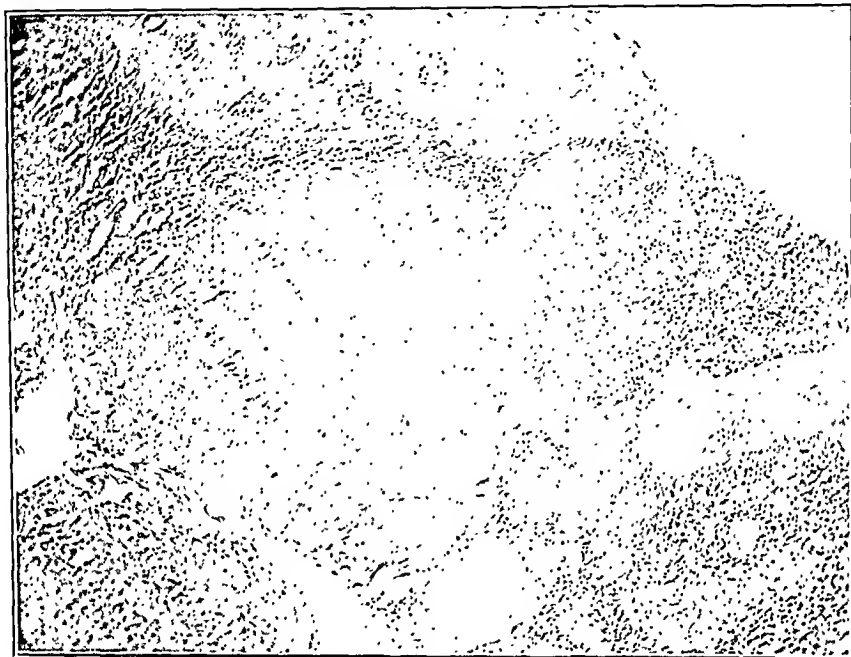


Fig. 1.—Carcinoma of cervix, low power, showing pale neoplastic cells invading the stroma, and leucocytic infiltration.

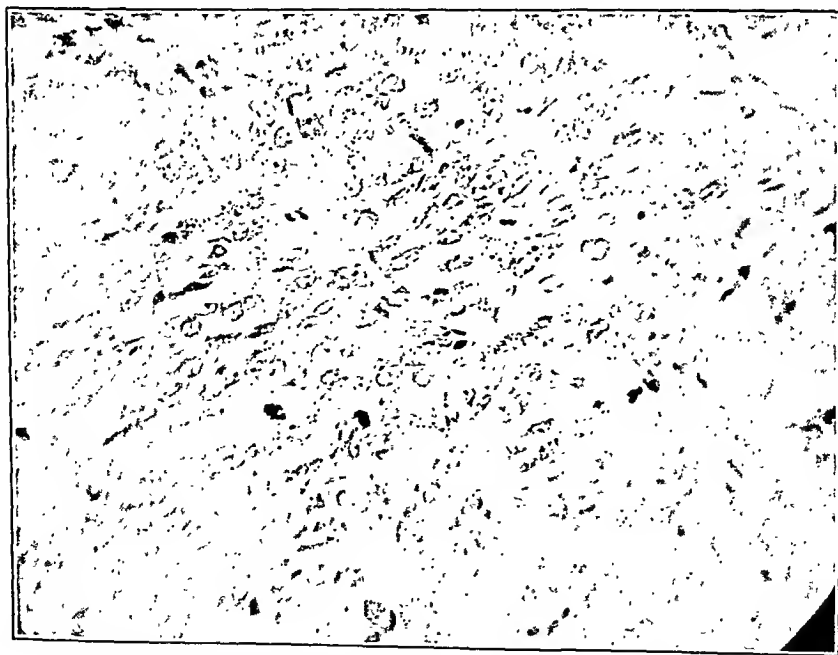


Fig. 2.—Carcinoma of cervix, high power, through neoplastic area showing large pale cells, prominent vesicular nuclei, and scattered mitotic figures.

## A SIMPLE TECHNIQUE FOR CRANIOTOMY ON THE HIGH AFTERCOMING HEAD

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WITH a high aftercoming head, such as in cases of hydrocephalus, it may be very difficult or impossible to do a craniotomy through the baby's mouth. The other alternative is through the occiput. However, attempt at direct perforation through the occiput of the high aftercoming head may greatly endanger the mother's soft parts and the bladder.

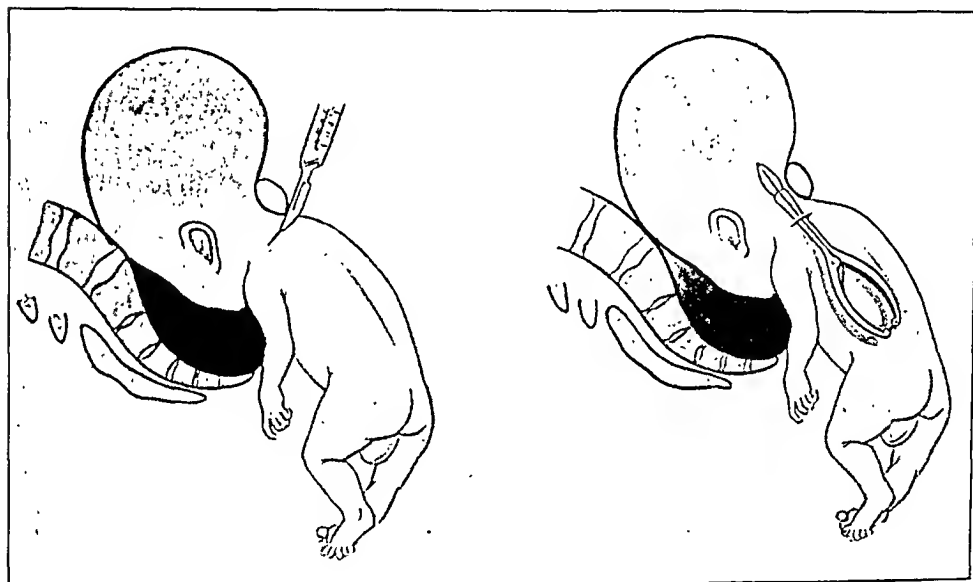


Fig. 1.

Fig. 2.

I have found the following technique useful. As illustrated in Fig. 1, a small transverse incision is made through the skin at the base of the neck. Then, as shown in Fig. 2, a Naegle perforator is introduced beneath the skin and tunneled to the suboccipital region. Here the perforation may easily be made into the cranial cavity through the occipital plate, without fear of the perforator glancing off the skull. After the cerebrospinal fluid escapes, there is enough collapse of the skull to make delivery easy.

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fourth day postpartum, a discharge from the baby's penis was noted. The baby was isolated and smears were taken. They were positive for gram-negative intracellular diplococci. The following treatment was instituted: Sulfanilamide gr.  $\frac{1}{2}$  every four hours and 10 per cent argyrol pack to glans penis four times a day. The baby was breast fed. The mother was isolated and smears taken from the lochial discharge were found to contain gram-negative intracellular diplococci. The mother and the father were both questioned concerning the possible source of the infection, and it was discovered that the husband acquired the disease after the mother had begun her antenatal care and had transmitted it to her late in the pregnancy. She carried the disease unknowingly. Treatment was also instituted in the mother and the disease was eventually arrested. The discharge from the baby's penis subsided rapidly. However, smears were positive for six weeks. Treatment was discontinued after three negative smears were obtained.

Because there are no available reports of a similar instance of urethritis in a male newborn, it is impossible to compare the course of this patient with others. In noting Villen's results in the treatment of newborn female genital infections, one would conclude that the sulfanilamide offers relief more readily.

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The author studied the mucosa of the uterine cervix with a view to determining the effect of hormones on it in the nonpregnant state. His material consisted of 99 specimens, of which 60 were obtained at autopsy, and 39 by operative means (12 hysterectomies and 27 cervical biopsies). The material was collected from newborn babies, young girls, mature women, and women past the climacteric.

The author found that in childhood and old age there is no evidence of hormonal action. During the reproductive years there are cyclic changes in the cervical mucosa. Corresponding to the proliferate phase of the endometrium, there is intense proliferation in the cervical mucosa. This proliferative phase is absent shortly before, during, and immediately after the menstrual flow, it reaches its greatest development at the time of ovulation, and accounts for the secretory changes observed in the cervix at that time.

In cases of amenorrhea due to atrophy of the uterine mucosa where there is no hormonal activity, cyclic changes in the cervix are absent. On the other hand, in cases of excessive hormonal action there is excessive proliferation of the cervix epithelium, in all probability caused by estrin.

The author experimentally investigated the effect of hormonal stimulation on the cervix in guinea pigs. He found that the cyclic changes were due to estrin but that progestin may have an inhibitory effect on estrin. He also observed that the passage of spermatozoa readily takes place by means of the motility of the sperm during the estrus phase when proliferation and secretion in the cervix are at their height. On the other hand, the transportation of sperm in this way is practically absent in the nonestrous phase and in castrates. If the estrous phase is reproduced in castrates by the administration of estrin, the possibility of the passage of spermatozoa is resituted.

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growth impulse is satisfied irrespective of the mother's diet, it seems most irrational to starve the mother during the last months of pregnancy in order to obtain a small baby. The correlations between weight of the child and the adequacy of the maternal diet are apparently not disturbed unless the women are extremely undersized or undernourished. In severe malnutrition of the mother leading to osteomalacia (adult rickets), it has been found that the fetus frequently shows marked signs of congenital rickets. There is also evidence indicating that qualitative deficiency of the diet may have a cumulative effect since infants from subsequent pregnancies are more affected than the first-born.

#### THE FOODS IN PREGNANCY

*Carbohydrates.*—The carbohydrate metabolism is deranged in normal pregnancy as indicated by the ease with which a glycosuria can be produced and the tendency for the blood sugar curves to be abnormal. Williams<sup>8</sup> found in repeated miscarriages that the blood sugar curve showed a "lag" and that there was often glycosuria but no diabetes mellitus. The use of insulin and a reduction in the carbohydrate intake to 150 or 200 gm. in such cases brought 11 out of 19 pregnancies successfully to term. The possibility of a disturbance in the carbohydrate metabolism as a cause of abortion should be kept in mind, but the very fact that these patients were seen early enough in pregnancy to permit proper supervision, introduces other factors which may have prevented abortion.

The daily intake of carbohydrates according to Shukers and others<sup>4</sup> is 300 to 340 gm., Coons,<sup>5</sup> 336 gm., and Sandiford and others,<sup>6</sup> 149 gm. in the thirteenth week, to 225 gm. in the thirty-eighth to fortieth week. In pregnancy when nausea and vomiting occur, it is advisable<sup>58</sup> to give a high carbohydrate diet every two hours. According to Harding and Potter<sup>9</sup> and other investigators, an abnormal carbohydrate and fat metabolism are factors in causing hyperemesis gravidarum. When severe toxemia of pregnancy is present or imminent, Dieckmann<sup>10</sup> suggests the use of an eclamptic diet which consists of only fruits and sweetened fruit juices.

*Protein.*—From the studies of Hunseher and others,<sup>11</sup> Wilson,<sup>12</sup> and Maey and Hunseher,<sup>13</sup> the nitrogen requirement during pregnancy for growth of the ovum, the uterus and mammary glands is about 135 to 145 gm. In addition to this special nitrogen requirement, the maternal organism tends to show a nitrogen retention in pregnant women of 200 to 400 gm. The daily protein intake necessary to provide for adequate nitrogen retention is, according to Coons and co-workers,<sup>5, 14, 15</sup> 70 gm., Adair and Dieckmann and others,<sup>17</sup> 75 gm., Sandiford and co-workers,<sup>6</sup> 90 to 100 and other investigators from 100 to 119 gm.<sup>4, 13, 16</sup>

The relation of protein content in the diet to the complication of toxemia in pregnancy, is not altogether clear. Strauss<sup>18</sup> contends that a diet low in protein may be the cause of toxemia in pregnancy. He bases his belief on the fact that his toxemic patients had low values for serum protein and that they were successfully treated by a high protein diet supplemented by vitamin B<sub>1</sub> and liver. On the other hand, it appears that in a small percentage of pregnant women the protein must be rigidly restricted during the latter part of gestation in order to avoid symptoms of toxemia.

# Department of Practical Problems in Obstetrics and Gynecology

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CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

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## DIETARY REQUIREMENTS IN PREGNANCY

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EVIDENCE was presented in a previous paper<sup>1</sup> to show the relationship between the fetal requirements and the maternal diet with respect to some minerals. The facts summarized in that study indicate clearly that certain dietary demands must be met to protect both mother and offspring from clinical pathologic changes during pregnancy. In this review of foods and accessory substances, it is hoped that the important dietary constituents discussed will permit of a nutritional margin sufficient to protect the mother, fetus, and infant even from early changes, subclinical in nature.

Although pregnancy under normal conditions is essentially a physiologic process, it makes special demands on the maternal organism, and diets adequate under ordinary conditions may fail to meet the increased requirements. Barborka,<sup>2</sup> after a study of American diets, concludes that many of our concentrated foods are low in vitamins, residue and alkaline minerals and high in carbohydrates and acid minerals. The foods that correct deficiencies common to our diet are milk, eggs, and leafy vegetables. These protective foods are highly essential during pregnancy and can prevent maternal and fetal morbidity due to demineralization and avitaminosis.

The average increase in weight<sup>3</sup> during pregnancy amounts to 9.7 kilo with a standard deviation of 4.3 kilo. Provided the patient is near the optimum for her height and age when conception occurs, we have for several years attempted to restrict the total weight gain to approximately 7.5 kilo (16.5 pounds) or a maximum weekly gain of 225 gm. (0.5 pound). This increase is equivalent to the weight of the fetus, placenta, amniotic fluid, and the maternal physiologic changes incidental to pregnancy.

The daily caloric intake required during this period varies greatly with the individual. The figures given<sup>4-6</sup> are from 2,000 calories in the early part of pregnancy to 3,500 calories in the last months. If obesity develops, the caloric intake must be reduced without decreasing the necessary minerals and vitamins. Efforts to control the size of the fetus near term by low caloric intake are generally unavailing and may do considerable harm if essential food constituents are withheld. Since the fetus in utero is essentially parasitic and the

infants, that the calcification of the bones was best where the maternal retention of calcium and phosphorus during pregnancy was highest. Toverud<sup>26</sup> found that the extent of calcification of fetal skulls depended upon the calcium content of the maternal diet. In all cases the mothers of infants with soft skulls either had a diet grossly deficient in calcium or had suffered from hyperemesis.

The calcium and phosphorus requirements of the mother in pregnancy are best satisfied by an intake sufficient to produce positive balances. Coons and co-workers<sup>15</sup> report adequate retentions with a mean intake of only 1.4 gm. of calcium and 1.69 gm. of phosphorus in Southern women. This intake, however, was not productive of adequate retentions in Chicago women receiving less sunshine. Toverud<sup>27</sup> found negative balances common in late pregnancy unless the intake of calcium was from 1.6 to 1.8 gm. per day. Dieckmann, basing his statement on balance studies of patients suffering from a calcium and phosphorus deficiency, advised that the diet in pregnancy contain at least 1.5 gm. calcium and 2.0 gm. phosphorus. Unpublished data by Adair and Dieckmann indicate that if the diet is a proper one an average intake of 1.3 gm. calcium and 1.4 gm. phosphorus resulted in a positive balance for almost all patients studied. Certain conditions may affect the optimum retention of calcium and phosphorus such as the percentage utilization of these minerals from the ingested food, the therapeutic administration of vitamin D and the effect of sunlight or irradiation with ultraviolet light.

The ratio of calcium to phosphorus in food is apparently of much less importance than the actual amounts. Coons and others<sup>15</sup> found that on diets containing a calcium-phosphorus ratio from 0.59 to 1.01, average of 0.86, the retention ratio varied from 0.14 to 2.36, average 1.21. These ratios demonstrate a selective power of the organism to retain calcium and phosphorus from the diet.

The foods rich in calcium are milk of animals and leafy vegetables. Apparently the best sources of calcium and phosphorus are milk and cheese. A quart of milk contains approximately 1.2 gm. of calcium and 0.9 gm. phosphorus. The leafy vegetables contain considerable calcium but the presence of oxalates forming insoluble salts lowers the percentage that can be utilized. "Apparently all other foods fall below the nutritive requirements of man and animals in calcium. Both McCollum and Sherman believe that the average American diet tends to be low in calcium and over-rich in phosphorus. The body is very sensitive to deprivation of calcium in the food and serious damage results to the bony structure and doubtless to other tissue if the diet does not contain sufficient amounts of this mineral."<sup>28</sup>

It is apparent that at least one quart of milk daily is necessary to bring the calcium intake up to the required limits. As substitutes it would take approximately 5 ounces of cheese or 12 average size oranges to have the same calcium content. Calcium salts, whether in the form of gluconate, lactate, or perhaps the best, dicalcium phosphate, are more expensive than milk and are usually excreted almost quantitatively in the urine and feces. It would require some 8 gm. daily of dicalcium phosphate,<sup>29</sup> because of the uncertainty of utilization, to equal the amount obtained from 1 quart of milk.

Apparently when foods containing sufficient calcium and phosphorus are ingested in pregnancy the magnesium requirement is also satisfied.

From extensive studies of serum proteins, Dieckmann<sup>19</sup> has not been able to substantiate these findings of Strauss. Several hundred patients have had serum protein determinations and only those patients with obvious nephrosis have had a low serum protein. He states that the serum protein concentration in normal pregnancy is 6.4 gm. per cent with a standard deviation of 0.4 gm. per cent, and in pre-eclamptic patients the average is 6.0 gm. per cent; in the vascular renal group, 6.6 gm. per cent; and in eclampsia, 6.7 gm. per cent. Unpublished work by Adair and Dieckmann based on an additional several hundred normal patients who were followed during pregnancy, indicate a serum protein concentration of 6.6 gm. per cent with a standard deviation of 0.4 gm. per cent. Furthermore, Dieckmann reports no improvement in toxemic patients who were placed on a diet containing 100 or more gm. of protein.

*Fat.*—Fat appears to be of primary importance as a carrier of essential vitamins A, D, E, and F. The optimal amounts in the diet for pregnant women are not known. According to Sandiford and others<sup>6</sup> the daily intake is from 107 to 113 gm., Coons<sup>5</sup> 103 gm., and Shukers and others<sup>4</sup> 112 to 139 gm. Complications in pregnancy directly associated with the intake of fat have not been clearly demonstrated.

*Fluids.*—Many workers agree that the ingestion of water in pregnancy should be liberal. Coons and others<sup>15</sup> found that the daily intake of water from foods and drinks totaled roughly 2,100 to 3,700 c.c. with the majority around 2,500 c.c. Thus the amount of fluid ingested when compared with the average daily total caloric intake was roughly 1 gm. of water per caloric in the food. We believe that sufficient water should be ingested to ensure a normal urinary output of 1,200 to 1,500 c.c. per twenty-four hours.

#### THE INORGANIC CONSTITUENTS IN PREGNANCY

The inorganic constituents calcium, phosphorus, magnesium, iron, copper, and iodine, in the following discussion are not necessarily taken up in the order of their importance but rather as a group having to do with ossification, hemoglobin formation and glandular disturbances.

There is conclusive evidence in the literature<sup>20, 21</sup> to show that animals on deficient mineral diets suffer loss of calcium and phosphorus from the body during pregnancy. While it is not to be hoped that equally direct information can be obtained for the mother and infant, yet evidence may be obtained on the fetus.

We have made determinations that show a 20 per cent increase in the calcium and phosphorus content in a seven-month-old fetus whose mother had been on a controlled mineral intake. In comparison it appears probable that all cases of fetal rickets<sup>22, 23</sup> due primarily to mineral deficient diets during pregnancy, would show hypomineralization. With respect to the mother, the first few infants born may not suffer to any extent, but one of us (W. J. D.)<sup>24</sup> has shown that frequent pregnancies and deficient nutrition have a cumulative effect. Apparently the maternal organism will mobilize calcium not only from the so-called reserves but continue until osteomalacia results and even then fetal rickets cannot be prevented. These findings indicate that differences in the degrees of calcification of fetal skeletons exist. Coons and Blunt<sup>25</sup> concluded, from x-ray examinations of bones of normal



whatever the previous condition or diet, if there is severe vomiting of pregnancy.<sup>35, 36</sup> In districts where pellagra is prevalent, the increased need of vitamin B<sub>2</sub> complex in pregnancy may unmask the latent disease. If pellagra occurs, an ample amount of vitamin B<sub>2</sub> (riboflavin), the P-P factor and nicotinic acid should be administered.

The food sources of the vitamin B complex are yeast, whole grain breads and oils, cabbage and carrots, leafy vegetables, egg yolk and oysters. To supplement these foods there are a number of concentrated vitamin B complex extracts besides the isolated vitamin B fractions available.

The importance of vitamin C, ascorbic acid, in pregnancy is not well defined. Apparently its deficiency interferes with normal ovulation and conception. Determinations of excretion of vitamin C in human urine indicate that the demand is increased in pregnancy. An ample supply is necessary for protection of the fetus and infant. The daily maternal intake recommended is approximately 75 mg. or 1,500 international units. The foods rich in this vitamin are citrus fruits, tomato, parsley, green or red peppers, uncooked cabbage and other leafy vegetables.

The administration of vitamin D, calciferol, in pregnancy is not a routine procedure in obstetric practice. However, the giving of therapeutic doses of vitamin D as found in cod liver oil and in concentrates, or exposure to sunlight is a most justifiable measure. Careful search of the literature seems to indicate that in the infant a correlation may exist between calcium deficiency, premature births, imperfect calcification, and birth trauma.

It may be said of the premature infant that, in spite of smaller size and easier head molding, birth is more hazardous. It is a known fact that intracranial hemorrhage occurs more frequently than in the full-term infant, probably primarily due to the softness of skull bones. The process of molding, however, does not depend on the softness of the skull bones but on the extent of overriding. It would appear then that firmness of the flat bones in the full-term infant protects the soft brain tissue and that good ossification is to be desired. Abel<sup>37</sup> observed, however, that administration of vitamin D tended to prolong the average duration of pregnancy in the human being about ten days. Along this line Toverud<sup>27</sup> made the interesting observation that on ample diets and vitamin D, except in June, July, and August, a lowering of the incidence of prematurity resulted.

It should be emphasized again that supplementing the diet of the mother with therapeutic doses of vitamin D from fish oils, concentrates or from the action of sunlight on the skin does not permit a decrease in the daily optimum calcium and phosphorus intake. Pregnant women should be given a teaspoonful of good grade cod liver oil, 350 to 400 international units, daily or the gradual exposure to sunlight or irradiation with ultraviolet light sufficient to maintain a slight tan.

Vitamin E, alpha tocopherol, appears to be of most importance in pregnant women subject to habitual abortion. Vogt-Møller<sup>38</sup> successfully brought 17 out of 20 such women to term by giving 40 drops of a vitamin E preparation, wheat germ oil, called "fertilan" thrice daily from the third to the seventh month and thereafter a dessertspoonful of wheat germ thrice daily. Subsequent vitamin E therapy<sup>39</sup> of 52 women suffering from habitual abortion resulted in 38 full-term living infants. Krohn and others<sup>40</sup> and Watson and Tew<sup>41</sup> report successful results in 75 per cent of women suffering from habitual and threatened abortion.

Coons and others<sup>15</sup> found that a daily intake of 0.35 to 0.45 gm. of magnesium was sufficient to give positive balances in the latter part of pregnancy.

The studies on iron metabolism in pregnancy reported in an earlier paper<sup>1</sup> indicate depletion of maternal stores with successive births. It has been shown that infant's hemoglobin values are normal at birth even where the mother's hemoglobin was low in pregnancy, but that the infant is more likely to develop a hypochromic anemia during the first year. Dieckmann and Adair have a number of cases where the cord blood hemoglobin and cell volume were well below normal if the mother had an anemia. Coons<sup>5, 30</sup> found that an average maternal intake of 15 mg. of iron a day permitted an average retention of 3.2 mg., sufficient to provide for the calculated needs of the mother and fetus. Studies of Adair and Dieckmann and others<sup>17</sup> confirm this work. Macy and Hunscher<sup>13</sup> found that 20 mg. of iron daily was the desirable amount in pregnancy. Apparently the larger amount gives a margin of safety since the availability of iron in different foodstuffs varies and absorption may be dependent upon gastric acidity. The foods rich in assimilable iron are liver, kidney, gizzards, red meats, raisins, prunes, apricots, and peaches. Iron salts and the vitamin B complex may be used to supplement the maternal diet, but their value is very questionable. Where the anemia is marked, transfusions of blood are indicated. In macrocytic anemia the necessity is not for minerals but Castle's extrinsic factor.

Information is very meager on the need of copper in pregnancy. From the studies of Sheldon<sup>31</sup> and Tompsett and Anderson,<sup>32</sup> it was found that the copper content of the blood was increased in pregnancy. Although copper deficiency may not occur frequently, the possibility is indicated since iron and copper together<sup>33</sup> are sometimes necessary to cure anemia when iron alone fails.

In certain sections of the country, where goiter is endemic, the iodine content of the diet must be considered. The amount of iodine needed in pregnancy may best be supplied by the routine use of iodized salt and seafoods, especially cod liver oil. These may be supplemented in special cases by calcium salts of iodized fatty acids.

#### THE VITAMINS IN PREGNANCY

The requirements for all vitamins appear to be increased in pregnancy. The most important to be discussed are vitamins A, B<sub>1</sub>, B<sub>2</sub>, C, D, and E.

With respect to vitamin A there is some work which would seem to indicate that the mucous membranes are made more resistant to infection when sufficient quantities of this vitamin are supplied. Maxwell<sup>34</sup> observed an infant born with keratomalacia which, he thought, was caused by the lack of vitamin A in the mother's diet.

The daily amount of vitamin A recommended for pregnant women is 9,000 international units. The richest diets provide scarcely 3,000 units. It may, therefore, be necessary to supplement the diets with the precursor carotene or fish oils high in vitamin A.

With respect to pregnancy, the interest in the fractions of the B complex is in B<sub>1</sub>, thiamin, the antineuritic factor and the B<sub>2</sub> complex. In animals, vitamin B<sub>1</sub> deficiency results in failure of conception, resorption of the fetus and frequent abortion and early death from a disorder closely resembling polyneuritis. Polyneuritis may occur,

Coons and Blunt<sup>25</sup> found that the greater the nitrogen retention, especially in the last stage of pregnancy, the more likely is lactation to be adequate.

From balance studies during lactation, conclusive evidence is presented in the literature to indicate that all foods are needed in more abundance. The specific effect on milk production by any one food is not easily determined in each instance. However, the ingestion of foods rich in carbohydrates does not appear to augment the yield of milk<sup>49, 50</sup> but tends to increase the fat content. The intake of foods rich in fat increased slightly the volume of milk with considerable increase in the concentration of fats.<sup>4, 50</sup> Deem<sup>50</sup> found that a high protein diet enriched by vitamin B increased the milk yield. Adair<sup>59</sup> stated that a high protein, balanced diet gave maximum milk production. Hunscher et al.<sup>16</sup> observed that subjects on high protein diets during pregnancy with daily nitrogen retentions of 3 gm., had later, during lactation, very high yields of milk. While quality in all three foods may be important, emphasis with respect to proteins is placed especially on dairy products.

The restriction of fluid intake may limit milk yield when all other necessary constituents are supplied in ample amounts. Macy and others<sup>51</sup> found that, beyond certain limits, the amount of liquid ingested by women did not affect milk yield.

The source of supply of minerals for lactating women is a good mixed diet containing one quart of milk daily. At the height of lactation as shown by a number of investigators,<sup>52, 53</sup> it may be difficult on this diet to procure a positive calcium balance. Apparently the daily calcium intake must be four times that present in the secreted milk to prevent body loss.<sup>47</sup> This ratio may be reduced by addition of cod liver oil and yeast to the mother's diet.<sup>54</sup> With respect to the minerals iron, copper, and manganese, many workers agree<sup>55</sup> that addition of these elements to the diet will not increase their concentrations in the mother's milk.

All the vitamins considered necessary in pregnancy are also of importance during the period of lactation, with special emphasis on an adequate amount of the B complex. However, an indiscriminate enrichment of the diet with vitamin concentrates is not advocated. The emphasis should be on the ingestion of mixed foodstuffs containing the natural source of the various vitamins.

As far as is known the concentrations of the various vitamins in the breast milk is largely dependent upon the vitamin content of the maternal diet. The vitamins that may more directly be connected with milk flow are B<sub>1</sub> and E.

There are considerable variations in the amount of foods and vitamins advocated by various investigators for the pregnant woman. We have attempted to list in Table I what we consider are the minimum requirements for the pregnant and lactating woman. If the patient is able to obtain a properly balanced diet containing milk, butter, eggs, meat, fruits, and vegetables, we do not prescribe any vitamins. It is not so much the actual amount of protein, calcium, phosphorus, iron, iodine, etc., in the diet as their assimilability by the patient. We have included the composition of milk, because it forms the basis of all diets requiring large amounts of calcium and phosphorus. Skimmed or better buttermilk may be used to decrease the fat content and thus reduce the caloric value.

Besides the preparation of vitamin E mentioned, many potent concentrates are on the market. In its natural state, E is found mostly in whole grains, egg yolk, green vegetables, and muscle meat.

Mattill<sup>42</sup> concludes an article on vitamin E as follows:

"More clinical evidence, obtained under carefully controlled conditions, is greatly needed to establish the usefulness of vitamin E therapy in abnormal human reproduction. Until this is at hand, attempts to produce a market for wheat germ oil among prospective parents generally are to be deprecated; so also is the suggested threat of national dietary sterility, *in view of the widespread distribution of vitamin E in the foods belonging in a well-balanced diet*. Individual cases of inadequacy, due perhaps to a faulty absorption or metabolism will not be understood until more is known about the chemistry and physiology of vitamin E."

Vitamin K is of no value to the pregnant or lactating woman but has been used in conjunction with bile salts in the treatment of a few cases of hemorrhagic disease of the newborn.<sup>43</sup>

The difficulty in determining the value in human beings of diets adequate in both food and vitamin content is illustrated by the following reports. Ross, Perlzweig, and co-workers<sup>44</sup> studied a group of pregnant women in an institution. One series for economic reasons received the general diet which was low in milk, butter, eggs, meat, fish, and fresh fruits. Another series had a well-balanced diet with adequate amounts of vitamins A, B complex, D, and E, as well as calcium, phosphorus, and iron. They concluded that there was no significant difference between the two series as to the incidence of toxemia or concentration of hemoglobin and serum protein.

A different aspect is given by the preliminary report of the British Minister of Health<sup>45</sup> who stated that among 4,446 mothers receiving special food, the puerperal death rate was 0.45; the maternal death rate from associated causes, 0.67; and the infant death rate (stillbirth and neonatal), 54. Among 9,040 mothers not receiving special foods, the corresponding rates were 3.54, 1.33, and 83, respectively.\*

#### THE FOODS IN LACTATION

The production of milk in the lactating mother does not require any expenditure of energy other than that contained in the milk itself, which in the human amounts to 700 calories per 1,000 c.c. Restricted muscular activity, freedom from worries, sufficient sleep, and an adequate diet promote milk secretion. However, the energy intake during lactation is materially increased over that in pregnancy. Studies<sup>4, 46, 47</sup> on the caloric requirements of lactating women indicate that 40 to 50 per cent of the total caloric intake may reappear in the milk.

An interesting point stressed by Garry and Stiven<sup>48</sup> in their excellent review is the fact that, "In farm stock it is well known that extra feeding beyond maintenance allowance during the last stage of pregnancy does not appear to affect the birth weight or subsequent growth of young animals, but has a very marked effect on milk yield." Along this line

\*Medical Research Council report to the Minister of Health: It is the opinion of the Committee that the results of the analysis of the present experiment should be awaited before further experimental observations are embarked upon. The Committee fear, however, that the practical difficulties in the way of securing precise comparability between the contrasted groups, having regard to the number of possibly relevant factors (age, parity, diet, medical supervision, etc.) are so great that it is unlikely that scientifically adequate conclusions would be reached.

## SUMMARY

Studies of the maternal diets in pregnancy and in lactation indicate that inadequate diets inevitably affect the well-being of the mother, fetus, and infant. Although deficiencies in diet causing morbidity of the fetus, such as rickets, hypoplasia of the teeth,<sup>56</sup> tetany<sup>57</sup> and anemia, may be corrected in early infancy, yet the first opportunity has been lost in not preventing the condition before it had a chance to develop. To correct these disorders of the fetus, emphasis should be placed on the proper maternal diet during the last trimester, provided that the mother has previously been in a good state of nutrition. It is interesting to note, however, that the production of an adequate supply of milk is dependent upon an optimum diet during the last trimester of pregnancy. The one important fact to be emphasized is that supplements of manufactured concentrates cannot be substituted for natural foodstuffs. In this day and age, when transportation of natural foodstuffs offers scarcely any problem, there should be no need for dietary disturbances in certain sections of this country due either to lack of food, vitamins, or to essential minerals.

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TABLE I. THE AVERAGE DAILY HUMAN REQUIREMENT IN PREGNANCY AND LACTATION BASED ON VARIOUS REPORTS

	MILK—1,000 C.C. OR 1 QT.	1-27 WK.	28-40 WK.	LACTATION
Protein	33.0 gm.	60.0 gm.	80.0 gm.	90.0 gm.
Fat	40.0 gm.	70.0 gm.	70.0 gm.	100.0 gm.
Carbohydrate	50.0 gm.	350.0 gm.	400.0 gm.	435.0 gm.
Calories	690.0	2,300.0	2,600.0	3,000.0
Calcium	1.2 gm.	0.7 gm.	1.4 gm.	1.4 gm.
Phosphorus	0.9 gm.	1.3 gm.	1.6 gm.	1.6 gm.
Magnesium	0.12 gm.	0.3 gm.	0.45 gm.	0.45 gm.
Iron	Liver, muscle, grapes	0.020 gm.	0.020 gm.	0.015 gm.
Iodine	Cod-liver oil	Iodized	Table	Salt
Vitamin				
A	Halibut liver oil	4,000.0 U.S.P.	9,000.0 U.S.P.	9,000.0 U.S.P.
B <sub>1</sub>	Yeast, whole grains	0.4 mg.—200 I.U.	0.8 mg.—400 I.U.	600.0 I.U.
B <sub>2</sub>	Yeast, whole grains, liver	1.5 mg.—600 I.U.	3.0 mg.—1,200 I.U.	3.0 gm.—1,200 I.U.
C	Citrus fruits, vegetables	20.0 mg.—400 I.U.	75.0 mg.—1,500 I.U.	75.0 mg.—1,500 I.U.
D	Fish liver oil, egg yolk	300.0 U.S.P.	800.0 U.S.P.	800.0 U.S.P.
E	Whole grains, lettuce	†	‡	‡

4 c.c. cod liver oil = approximately 3,000 units A and 300 units D.

40 c.c. orange juice = approximately 400 units C.

# Editorial

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## The Prevention of Syphilis in Marriage

IN THE hope of reducing the incidence of marital and congenital syphilis, several states have included in their statutes specific laws calling for compulsory serologic tests before contemplated marriage and during pregnancy. These laws have been in force too short a time to make possible any evaluation of their efficacy or of their general public approval. However, it is of interest to note that records now available show a definite trend in their acceptance.

Sixteen states now have premarital examination laws, according to *Health News*, the official organ of the New York State Department of Health, and in six states every pregnant woman must have a serologic test for syphilis at the time of the first medical examination. The former are made ineffectual to some degree by couples who marry outside of these states but steps are being taken to void this. Surveys in six states suggest that marriages at first undergo a decrease but this is only temporary and evidently, after the purpose of the law is understood and appreciated, there is no reduction in the usual rate. In five states in which premarital tests were studied, the reactions were positive in 1.3 per cent.

The experience of New York State, exclusive of New York City, with tests in early pregnancy is of interest. During a nine months' period, 188 cases of syphilis were discovered among expectant mothers. As near as can be determined from laboratory records, the incidence of positive tests was 1.8 per cent. One-half of the mothers found to have syphilis were under 28 years of age and only one-fourth of the tests were made before the fifth month.

Obviously the introduction of this legal protective measure against the transmission of congenital syphilis is of value in case finding and, as time goes on, it will become recognized as an important and effective public health measure. A more universal adoption throughout the country of similar laws seems necessary to develop more satisfactorily the attack against this debilitating disease, which constitutes only a part of the larger movement to root out one of the most serious plagues of mankind. The obstetrician has an important function to perform and he need no longer hesitate to employ the necessary serologic tests as a part of the routine prenatal examination, for the public is rapidly acknowledging the desirability of such measures for its protection.

In the medical profession, however, there is by no means an unanimity of opinion in favor of the legislation as so many factors are involved. Snow<sup>1</sup> has recently declared himself in the affirmative; Nelson<sup>2</sup> the negative. Stokes and Ingraham<sup>3</sup> have given a lengthy discussion without assuming a positive or negative opinion, while Kolmer,<sup>4</sup> after a thorough

<sup>1</sup>Snow, W. F.: *Am. J. Syph., Gonorr. & Ven. Dis.* 23: 277, 1939.

<sup>2</sup>Nelson, N. Q.: *Am. J. Syph., Gonorr. & Ven. Dis.* 23: 288, 1939.

<sup>3</sup>Stokes, J. H., and Ingraham, N. R.: *J. A. M. A.* 112: 1133, 1939.

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**Grodberg and Carey: Sulfanilamide in the Treatment of Gonorrhea in the Female,** New England J. M. 218: 1092, 1938.

All of the patients included in this study were treated with sulfanilamide, the average daily dose being from 20 to 30 gr. for a four- to six-week period.

In every case they demonstrated the gonococcus intracellularly in smears of the exudate stained by Gram's method.

This treatment was the only one utilized, and the patients were told not to take medicated douches except in special cases. Originally these patients were seen three times a week, but later at weekly visits. They were advised to refrain from coitus and the use of alcohol.

The type cases have been acute endocervicitis, acute urethritis, vulvovaginitis, both adult and juvenile types, and acute pelvic inflammatory disease. The authors treated a few patients in various stages of pregnancy.

In less than one week, usually about three to four days, there was subjective improvement. The smears taken at about one week after the onset of medication showed fewer gonococci, with the organisms situated extracellularly.

The purulent nature of the smear continued, but in from seven to ten days gonococci were absent. Acute masses, both tubo-ovarian and vulvovaginal, resolve in about ten to fourteen days.

The drug was ineffective in the majority of cases of infantile vulvovaginitis, utilizing both topical and oral sulfanilamide medication. There were 85 per cent cures in the authors' adult group.

All observers report a lower percentage of cures in women.

J. P. GREENHILL.

**Alexin and Herrnberger: Investigation of the Vaginal Content of Newborn and Nursing Babies,** Zentralbl. f. Gynäk. 62: 9, 1938.

The writers found that characteristic changes in the vagina of newborn babies occurred during the first few weeks of life. In the first week vaginal smears revealed the top layer of cells of the vaginal mucosa. During the second week the cornified cells disappear and cells from the deeper layers appear.

On the second and third days bacteria and leucocytes are found. The latter disappear when the cornified cells make their appearance and they return when the cells of the deeper layers are found in the smears. The bacterial flora consists of Döderlein bacilli until the middle of the second week after which there is a mixed coccal flora.

J. P. GREENHILL.



Kolmer knows of no valid or important reasons *against* the legal requirement of blood tests during pregnancy or at delivery. Falsely positive reactions are no more likely to occur than in the case of men and nonpregnant women with acceptable methods skillfully conducted. It is true that difficult situations may be created in the case of syphilitic husbands infecting their wives without the knowledge of the latter but, after all, no physician should be a party to any arrangement that leaves an unsuspecting wife to her fate. It is also true that women objecting to blood tests during pregnancy may elect to be delivered by a midwife or neglect calling a physician until in labor. For these reasons, Kolmer believes that the results of a blood test during pregnancy or at delivery should be required to be reported on all birth certificates.

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Heaton, Claude Edwin: *Prenatal Care*, M. Clin. North America, November, 1937, p. 1859.

Prenatal care implies constant and efficient supervision with hospitalization for those conditions too serious to be adequately coped with at home. The diagnosis and management of intercurrent or associated conditions complicated by pregnancy necessitate individualization and the aid of internal medicine. Nutritional aspects of pregnancy deserve consideration in the prevention of deficiency states and congenital syphilis is a preventable disease. An effort should be made to prevent eclampsia by prompt attention to signs of hypertensive vascular disease evidenced by a progressive rise of the diastolic blood pressure, proteinuria, upset water balance and spastic changes in the retinal arterioles. Ante-partum bleeding necessitates ruling out placenta previa. Fetal malposition, especially breech presentation, should be corrected where possible. The relative size of the birth canal and passenger should be determined in advance for possible disproportion and for this purpose roentgenography should be utilized.

J. P. GREENHILL.

Young, H. H.: *Diverticulum of the Female Urethra*, South. M. J. 31: 1043, 1938.

There are a case report, a review of the literature, and a brief discussion of this anomaly.

In a 57-year-old multipara who presented a history of painful, frequent urination with difficulty in starting the stream, a rounded elastic mass 3 cm. in diameter was found projecting into the vagina from behind the urethra. Cystoscopic examination revealed an entirely normal bladder. In the floor of the urethra, however, there was noted a small opening which led into a periurethral pouch of a diameter of approximately  $2\frac{1}{2}$  cm. The relations of this structure to the bladder were demonstrated by cystourethrogram. Surgical removal was successfully accomplished by transverse incision in the vaginal mucosa, dissection of the pouch, and transverse closure of the defect in the floor of the urethra by continuous suture. Patient was relieved of her symptoms.

True congenital diverticuli of the female urethra are rare, and usually occur in the median portion of the urethra. Their etiology has not been definitely established, but the possible causal relationship to Müllerian and Gärtner duct remnants has been mentioned. Despite the fact that urethral glands are not commonly found at the usual site of the development of the diverticuli, etiologic importance has been claimed for them by some writers.

In the absence of complications such as suppuration, calculus formation, or mechanical interference with urination or coitus, there may be few symptoms. It is suggested that in some cases the condition is overlooked or incorrectly diagnosed as cystocele.

ARNOLD GOLDBERGER.

discussion of reasons for and against legally required premarital and pregnancy blood tests, finds himself in favor of premarital examinations, including blood tests, and certainly in favor of blood tests during pregnancy or at delivery when conducted by methods possessing the maximum of sensitivity consistent with specificity and by serologists of skill and experience. He gives the following ten reasons in *favor* of such legally required *premarital* examinations:

1. Because marriage inevitably involves syphilitic men and women in view of the high incidence of the disease.
2. Because they will tend to lower the incidence of syphilis.
3. Because they are the most valuable single means for the detection of the disease, especially after the primary, or chancre, stage.
4. Because of the inadequacy or absence of a history of infection.
5. Because of the inadequacy of clinical detection of the disease.
6. Because they will reduce the incidence of syphilis to spouse and children.
7. Because they will reduce the incidence of the economic hazards of marriage from incapacity or early death of the spouse.
8. Because they will reduce the incidence of divorce.
9. Because they will greatly encourage the thorough treatment of syphilis.
10. Because they are an excellent phase of the educational program against syphilis.

Four reasons are offered, however, *against* legally required *premarital* examinations as follows:

1. Because premarital blood tests may give nonspecific or falsely positive reactions.
2. Because positive blood reactions as the only evidence of syphilis may not always indicate a danger to marriage, especially in the case of thoroughly treated chronic syphilis.
3. Because they may discourage marriage and promote sexual promiscuity.
4. Because premarital blood tests alone may not detect syphilis, especially in its incubationary and primary stages.

Five reasons are given in *favor* of blood tests during *pregnancy or at delivery* as follows:

1. Because they afford an excellent opportunity for detecting syphilis in both married and unmarried women.
2. Because the detection and treatment of syphilis in pregnancy increases the chance of the birth of a nonsyphilitic child, with a reduction in the number of miscarriages and in infant mortality.
3. Because the detection of syphilis in pregnancy results in the treatment of the mother, especially during subsequent pregnancies.
4. Because the detection of syphilis in pregnancy may result in its detection and treatment in the child after birth.
5. Because the detection of syphilis during pregnancy may lead to its detection and treatment of the father and other children.

structures and other bodily systems. After portraying various diagnostic methods, the subject of radiation is fully considered, and there is a chapter on other physical methods. Typical operative procedures are described, and there is a short discussion of the relationship of vitamins to pelvic physiology, and a section regarding the sedimentation time in pelvic diseases.

Weibel emphasizes the psychic aspects of adolescence and the menopause, and cautions against too great a reliance on hormones to control symptoms of the latter phase. Abnormal constitutional types and tendencies are succinctly described, and Weibel very cleverly correlates their effect upon the genital apparatus as well as their relation to pelvic deficiencies. The diagnoses of developmental anomalies of the pelvic organs are aptly illustrated by radiographs following lipiodol injections.

The section on inflammatory diseases of the vulva is beautifully illustrated by a number of colored plates. Weibel regards kraurosis as a later stage of leucoplakia. He regards vaginismus as a purely psychic condition. In a discussion of non-inflammatory diseases of the uterus he considers endometriosis on the heterotopic theory of Robert Meyer. Apparently myomectomy is not an operation of choice in this clinic. The total extirpation of the myomatous uterus is practiced consistently in opposition to supravaginal hysterectomy. Roentgen therapy of uterine myomas has, in Weibel's opinion, a very limited field.

Gradation of carcinoma in relation to treatment apparently gives the same results as obtained in this country. Both preoperative and postoperative roentgen therapy are used in connection with the radical operation. Weibel does not feel that there is much final difference in the results of operative or radiation therapy, if the primary operative mortality for the radical operation be taken into consideration. Weibel lays stress on the Schüller method of diagnosing carcinoma of the cervix and does not feel that the true picture is always revealed by test excision.

A novelty in illustrating changes in position of the uterus consists in the use of a large number of suitable frozen sections of pelves showing various types and forms of prolapse. Sterility and contraception are discussed in consecutive chapters. Weibel believes more information is gained from lipiodol salpingographs than from perturbation of the tubes. He also feels that sterilization should only be practiced under the strongest indications, and after consultation.

There is a full consideration of the technique of radium and roentgen therapy, and other types of physical therapy.

While the section on operative therapy is limited, typical operations are beautifully illustrated. The book serves as an excellent companion volume to the section on obstetrics; together they may be regarded as a well-balanced exposition of the healing art for women.

—Philip F. Williams.

The sheer artistry of both text and illustrations of the second edition of *Control of Conception*<sup>4</sup> by Robert Latou Dickinson, makes its perusal a delight. This is a most important contribution to preventive medicine which, in this edition, has been brought fully up to date. Throughout, the author has sought for security and simplicity. Every phase of the subject is covered; effectiveness, the variations necessary to meet different general and local conditions such as, for example, the bride, extreme ignorance and poverty, as in the coolie, the treatment of patients with prolapse, are all taken up. This is a true source book of sex anatomy, methods of contraception and allied subjects. It fully meets with the crying need for help to the physician, and through him, to the laity.

—R. T. Frank.

A short brochure on the *Vaginal Diaphragm*<sup>5</sup> by Clark, contains full details on its use as well as that of contraceptive jelly, the sole method discussed. Every

<sup>4</sup>*Control of Conception.* By Robert Latou Dickinson, M.D., Former Clinical Professor of Obstetrics and Gynecology, Long Island College Hospital, etc. A clinical medical manual with numerous original illustrations by the author. Second edition, 390 pages. Williams & Wilkins Company, Baltimore, 1938.

<sup>5</sup>*The Vaginal Diaphragm.* By Dr. Le Mon Clark, Chicago. Illustrated, 107 pages. The C. V. Mosby Co., St. Louis, 1939.

# Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

## Review of New Books

### Gynecology

For the first time both the investigator and the clinician have at their disposal a monograph which covers the physiology of the uterine muscle.<sup>1</sup> The author has contributed much to our knowledge by his personal investigations, and in addition has carefully assembled a continuous exposition of all that has been gained from the work of other physiologists.

The clinician and the obstetrician will find many of the basic causes which produce sterility, abortion, or other disturbances of pregnancy, and explanations of some of the other manifestations of functional disturbances of the female genital tract.

Even if the reader does not desire to read this book from cover to cover, he will be able to refer to it in connection with various problems which constantly confront the investigator and the clinician.

—R. T. Frank.

Witherspoon has written a *Clinical Pathological Gynecology*,<sup>2</sup> in which he correlates the gross and microscopic pathology with clinical interpretation of the etiology, symptoms, diagnosis, treatment, and prognosis of each condition. This should prove of value to medical students, particularly as the combined viewpoint emphasizes the importance of gross and microscopic pathology in connection with clinical knowledge. The text is short, very up to date and while it contributes nothing essentially new, the presentation is good. The numerous illustrations, 271 in number, make this a very useful book for teaching purposes. While the microphotographs are practically all original, the large number of the gross pictures are from well-known sources which are duly credited. The book will prove of great service to teachers, particularly those whose clinical material and experience are limited, in preparing an excellent course for students. The reproduction of illustrations and bookmaking are faultless.

—R. T. Frank.

After a lapse of two years Weibel offers the gynecologic volume of his *Lehrbuch der Frauenheilkunde*<sup>3</sup> which completes his presentation of the subject. In this second volume, which deals mostly with gynecology, he develops more fully the physiology of the female pelvic organs in considering the various alterations and dysfunctions. In a logical manner the text carries through tumor formations, displacements, inflammations, and the relationship of the genital organs to the surrounding

<sup>1</sup>Physiology of the Uterus. With Clinical Correlations. By Samuel R. M. Reynolds, Fellow, John Simon Guggenheim Memorial Foundation, University of Rochester School of Medicine and Dentistry, Associate Professor of Physiology, Long Island College of Medicine, Brooklyn, N. Y. Illustrated, 447 pages. Paul B. Hoeber, Inc., 1939.

<sup>2</sup>Clinical Pathological Gynecology. By J. Thornwell Witherspoon, Formerly Associate Professor of Experimental and Pathological Gynecology, Indiana University Medical Center, Indianapolis. Illustrated with 271 engravings, 400 pages. Lea & Febiger, Philadelphia, 1939.

<sup>3</sup>Lehrbuch der Frauenheilkunde, in zwei Bänden. Von Prof. Dr. W. Weibel, Vorstand der II. Universitäts-Frauenklinik in Wien. Zweiter Band: Gynäkologie. Urban & Schwarzenberg, Berlin und Wien, 1939.

offers much information concerning osteomalacia, "which is fairly common in North India but practically unknown in South India."

In a textbook of obstetrics, which takes cognizance of such modern information as Caldwell-Moloy's classification of pelves, warns against Schultze's swinging, mentions the usefulness of Willett's forceps in treatment of placenta previa and describes the value of sulfanilamide, one is somewhat surprised to find in connection with the therapy for exaggerated vomiting of pregnancy, recommendations such as oral administration of cerium oxalate, cocaine, Lugol's solution, dilute hydrocyanic acid and cocaineization of the eroded cervix.

The author expresses precisely his own views and advocates the methods which have proved most useful in his own hands. In this connection his interesting observation may be mentioned that in cases of hydatid mole, the chances of an invasion of cells and thus for a chorioepithelioma are greater if the vesicles of the mole are very small.

As far as style of language, arrangement of material and typography are concerned, the volume deserves unstinted praise.

—Hugo Ehrenfest.

The close relation of *Midwifery*<sup>10</sup> by Ten Teachers to *The Abnormal in Obstetrics*<sup>11</sup> by Sir Comyns Berkeley, Victor Bonney and Douglas MacLeod makes it convenient, if not essential, to discuss both these volumes conjointly.

After but three years it became necessary to prepare a new sixth edition of the widely appreciated *Midwifery* by a slightly altered group of obstetricians, all teachers in London. In regard to this well-known book it will suffice to state that many eliminations and additions have been made both in the text and in the illustrations, undeniably enhancing the value of this compact textbook. It seems, however, noteworthy that for the first time illustrations of the low cervical cesarean section have been included. Willett's forceps, attached to the fetal scalp for the purpose of traction which, we believe, is but rarely used in this country, is mentioned and recommended, e.g., in connection with the treatment of hemorrhage from placenta previa or again for lifting the fetal head out of the pelvic inlet in the low cesarean section.

As well characterized by the volume just reviewed British textbooks of obstetrics as compared with the respective American standard textbooks in general limit themselves to the presentation of essential facts. For this reason it becomes necessary also to write books useful "to those ambitious of passing one of the higher examinations in obstetrics" or "to those in whose work midwifery plays an important part." We feel that *The Abnormal in Obstetrics* in this country will appeal particularly to the latter group. The deliberate omission of details in regard to anatomy, physiology, and operative procedures as useless repetition readily explains the almost complete absence of illustrations. The topics authoritatively discussed among others are Sterility, Endocrine Anomalies, Toxic States, Complicating Diseases of the Mother, Anomalies of the Genital Tract, Complications During Delivery, Puerperal Sepsis, Diseases of the Breast, Diseases, Injuries and Malformations of the New-Born. The two concluding chapters are devoted to Blood Transfusion (illustrated) and Analgesia, respectively.

The volume begins with a somewhat startling sentence: "Pregnancy is a state induced by a neoplasm." In some aspects the rapidly growing fetus might be compared with a neoplasm, but we regret that in pointing out the many similarities between these two conditions the authors fail to emphasize the obvious fact that unlike any other neoplasm the fetus exerts a definitely beneficial, stimulating effect on the function of almost all maternal organs. Thus pregnancy is probably not

<sup>10</sup>*Midwifery*. By Ten Teachers, under the direction of Clifford White, Obstetric Surgeon, University College Hospital, etc. Edited by Sir Comyns Berkeley, Clifford White and Frank Cook. Sixth edition, 262 illustrations and 9 color plates, 676 pages. William Wood & Company, Baltimore, 1938.

<sup>11</sup>*The Abnormal in Obstetrics*. By Sir Comyns Berkeley, Consulting Obstetric and Gynaecological Surgeon of the Middlesex Hospital, London, etc., Victor Bonney, Consulting Obstetric and Gynaecological Surgeon to the Middlesex Hospital, etc., and Douglas MacLeod, Assistant Obstetric Surgeon, St. Mary's Hospital, etc. First edition, six illustrations, 525 pages. William Wood & Company, Baltimore, 1938.

detail is entered into for the benefit of the physician. The special aim of the book is to enable the physician to instruct patients correctly.

—R. T. Frank.

In Quinet's *Histophysiology of the Menstrual Cycle*,<sup>6</sup> two-thirds of the monograph is devoted to a very careful analysis of the morphologic, physiologic, and biologic literature of the subject. His personal observations deal with uterine biopsy and vaginal smears, particularly in castrates, and the effect upon these of hormone therapy. While the monograph contains nothing new, it is a very excellent and well-gotten up résumé.

—R. T. Frank.

Bourne and Williams' *Recent Advances in Obstetrics and Gynaecology*<sup>7</sup> has reached the fourth edition. As previously, very selected subjects have been chosen for exposition. For example, under obstetrics, remarks on ante-partum hemorrhage, pyelitis, puerperal sepsis may be mentioned; under gynecology, cancer of the uterus, sterility, prolapse, sympathectomy, and the sex hormones. The book does not replace the American Year Books, as it is not as comprehensive as these. On the other hand, the subjects are taken up in much greater detail. The illustrations of the Manchester operation might well bear redrawing as they do not illustrate the technical steps adequately. The reviewer must take exception to the statement on page 258 that "In any case, to form an idea of urinary oestron excretion, in the presence of abnormality, it would be necessary to estimate the excretion every day for a month, which is manifestly impossible in clinical work." Certainly in many hospitals in this country as well as abroad, innumerable cases have been investigated over periods of a month.

—R. T. Frank.

*Feminine Hygiene in Marriage*<sup>8</sup> is a short book written by a layman. It contains "information to aid the married woman to meet the special problems of her sex." It is a "home" book for the laity, containing true information which, however, might be readily misinterpreted. For example, it lauds vaginal tampons instead of napkins, with which advice most physicians would disagree.

—R. T. Frank.

## Obstetrics

The most characteristic features of this new work, entitled *Clinical Obstetrics*,<sup>9</sup> are due to the fact that its author, Dr. Mudaliar, is Professor of Obstetrics in the University of Madras. His book is distinctly adapted to specific local needs both in teaching and in practice. Problems and methods of treatment of special practical importance are stressed and described in detail. Thus in the extensive discussion of diseases complicating pregnancy we find a special chapter devoted to Tropical Diseases. Since "pernicious anemia of pregnancy is very common in tropical countries" the 12 pages assigned to anemia include a description of the methods of hematologic examinations. The high incidence of malaria among pregnant women in India easily explains why in the description of differential diagnosis of eclampsia the item of Cerebral Malaria has been included. It is only natural that the volume

<sup>6</sup>*Histo-Physiologia do Ciclo Menstrual*. Par Dr. Antonio A. Quinet. Oficinas Gráficas de A. Nolte, Rio de Janeiro, 1938.

<sup>7</sup>*Recent Advances in Obstetrics and Gynaecology*. By Aleck W. Bourne, Obstetric Surgeon to St. Mary's Hospital, etc. and Leslie H. Williams, Senior Obstetric Surgeon to Out-Patients, St. Mary's Hospital, etc. University of Cambridge. Fourth edition, with 98 illustrations, 366 pages. Blakiston's Son and Co., Philadelphia, 1939.

<sup>8</sup>*Feminine Hygiene in Marriage*. By A. F. Niemoeller, A.B., M.A., B.S. Illustrated, 155 pages. Harvest House, New York, 1938.

<sup>9</sup>*Clinical Obstetrics*. By A. Lakshmanaswami Mudaliar, Professor of Obstetrics, University of Madras, Medical School, etc. With 204 text illustrations and 9 in color, 819 pages. Oliver and Boyd, Edinburgh, Tweeddale Court, 1938.

It is obvious that in the hands of such experts the numerous problems constituting the science and practice of obstetrics are presented both exhaustively and authoritatively. As is practically inevitable in a work of collaboration of this sort, there can be noticed a certain disproportion in space given to the consideration of some topics. The American reader cannot fail to observe that in German obstetric practice relatively little importance is assigned to blood transfusions or roentgenography, especially in its applicability to pelvimetry. Possibly for this reason no reference is made to the work of Caldwell or Thoms. An outstanding feature of this volume is the abundance of excellent illustrations, particularly of those reproducing natural color photographs.

—Hugo Ehrenfest.

Devraigne has given a glance at obstetrics throughout the ages.<sup>14</sup> In it he has attempted to condense the three big volumes written by de Siebold and Hergolt which cover the entire history of obstetrics. The illustrations are mainly from Witkowski. He starts with the midwife in the Bible, pre-Hippocratic and Hippocratic medicine, mentions that Celsus described version and embryotomy. Soranus was the first one to use podalic version to extract the live fetus. The entire history of obstetrics is divided into eleven epochs. The text is short, profusely illustrated, and forms a handy epitome.

—R. T. Frank.

The second edition of Burkhard's *Obstetric and Gynecological Therapy* with inclusion of drug treatment<sup>15</sup> is designed for rapid orientation of the problems which confront the practitioner. The material is arranged alphabetically. Big interventions are just indicated, while those which fall into the working sphere of the general practitioner are described in detail. Many of the methods are no longer acceptable here, as for example, dilatation with laminaria in inevitable abortion, or irrigation of the cavity of the uterus with antiseptic solutions after emptying. Thirty-three closely printed pages cover the numerous drugs suggested, the vast majority of which are trade preparations quite unknown in this country.

—R. T. Frank.

The series on Urology edited by Boeminghaus, cover two special aspects.

Ottow describes the *Urological Indications for Interruption of Pregnancy*.<sup>16</sup> The monograph of 27 pages describes various urologic complications of pregnancy, whether they require or do not require interruption. Throughout, the conservative viewpoint is emphasized.

—R. T. Frank.

Rubritius, in the compass of 22 pages, takes up the *Spasm of the Vesical Sphincter*.<sup>17</sup> The hypertonic sphincter may cause the same symptoms and bi-effects as prostatic hypertrophy. The cause may be local or from the spinal cord. For the cure he advises his own operation, requiring a wedge-shaped open excision of the sphincter ring in preference to transurethral section.

—R. T. Frank.

De Moraes has written a book for expectant mothers of which this, *Sa Maternidade*,<sup>18</sup> is the second edition. It is simple and contains both prenatal and postnatal advice.

—R. T. Frank.

<sup>14</sup>*L'Obstétrique à Travers les Ages*. Par L. Devraigne, Accoucheur de Lariboisière, etc. With 77 illustrations, 138 pages. Gaston Doin & Cie., Paris, 1939.

<sup>15</sup>*Geburtshilfliche und Gynaekologische Therapie, mit Einschluss der Heilmittel*. Von Dr. Georg Burkhard, o. Professor der Geburtshilfe und Gynaekologie, Universität Wuerzburg. Second revised edition, 200 Seiten. Verlag von Ferdinand Enke, Stuttgart, 1938.

<sup>16</sup>*Schwangerschaftsunterbrechung aus Urologischer Indikation*. Von Professor Dr. B. Ottow in Berlin. 27 pages. Verlag von Georg Thieme, Leipzig, 1939.

<sup>17</sup>*Die Hypertonie des Inneren Blasensphinkters*. Von Professor Dr. Hans Rubritius in Wien. 22 pages. Verlag von Georg Thieme, Leipzig, 1938.

<sup>18</sup>*Sa Maternidade*. Par Prof. Arnaldo de Moraes. Second edition. Graphica Sauer, Rio de Janeiro, 1938.

correctly qualified as standing alone among all physiologic processes in that, while the others serve the good of the individual, "reproduction is exercised for the benefit of the race at the cost of the individual." The cost, admittedly, is still too high and might well be expected to become lessened if every practitioner would become thoroughly familiar with all the important facts presented in this volume.

—Hugo Ehrenfest.

Beginning this review with a summary, which customarily concludes it, we state that this *Text-Book of Obstetrics*<sup>12</sup> of the Queen Charlotte's Maternity Hospital in London, now appearing in its fifth edition, admirably fulfills its purpose of setting forth precisely the views held and methods practiced by its clinical staff. Confusing descriptions of theories or varieties of opinion and treatment are avoided.

Obviously one looks for striking and noteworthy differences in British and American practice. In all the more important questions they are hardly noticeable, though careful reading of the book leaves one with the definite final impression that British obstetric methods are more conservative. Patients still are examined and delivered in the side position. Episiotomy, described not in connection with delivery of the head but in the section entitled Abnormal Labor, is referred to as "sometimes advisable." The treatment of even severely toxemic patients is strictly limited to dietetic management (detailed diet lists are given) and other therapeutic procedures, as commonly applied in our country, seem to be instituted only after convulsions have set in. Great stress is put on Stroganoff's conservatism in dealing with eclampsia. Chiefly for the purpose of avoiding unnecessary cesarean sections a clear and extensive discussion of trial labor is offered. A relatively large amount of space (over 50 pages) is devoted to an exhaustive consideration of puerperal sepsis. Sulfanilamide preparations "show great promise of completely altering the outlook, at any rate in infections with the hemolytic streptococcus."

No percentage figures are given for the incidence of forceps extractions, cesarean sections or other operations in the Queen Charlotte's Maternity Hospital but, judging from the entire tone of the volume and the quoted reference to episiotomy, there can be no doubt that our operative interference is decidedly higher. Thus naturally the question suggests itself: Does the evident conservative trend of British obstetrics yield better results?

Maternal mortality figures, as is well known, are not directly comparable but, in regard to maternal loss, disappointment is expressed in the fact that it has not been noticeably decreased within the last forty years and still stands for England and Wales at about 4 per 1,000 births (Denmark 2.6; Norway 2.8). In contrast the infant death rate during the same period of time has declined from 156 to the present rate of 59 per 1,000 births.

This in itself would seem most satisfactory were it not for the subsequent statement that in a recent series of breech labors in this hospital "the gross fetal and neonatal mortality reached the alarming figure of 37 per cent." So it seems that good obstetrics lies somewhere between British conservatism and American radicalism.

—Hugo Ehrenfest.

In the course of a few years it became desirable to revise extensively this new fifth edition of *Stoeckel's Textbook of Obstetrics*.<sup>13</sup> Considerable obsolete matter was eliminated, a good deal of new material added and numerous alterations made in the illustrations. The death of Professor von Franqué necessitated some changes in the staff of the nine collaborators which includes most of the heads of large German women's clinics.

<sup>12</sup>The Queen Charlotte's Text-Book of Obstetrics. By Members of the Clinical Staff of the Hospital. Fifth edition, with 4 colored plates and 293 text figures, 668 pages. J. & A. Churchill Ltd., London, 1938.

<sup>13</sup>Lehrbuch der Geburtshilfe. Herausgegeben von Professor Dr. W. Stoeckel, Universitäts Frauenklinik in Berlin. Fifth revised edition, with 639 illustrations, the most of which are colored, 1054 pages. Verlag von Gustav Fischer, Jena, 1938.



whole, successful. It is impossible in the scope of a review, particularly of a second edition, to give even a slight résumé of the content. In speaking of the origin of the gonads, it is said "the gonad-forming area contains the fundamental material for the formation of the sex cells." Yet removal of the germ cell crescent of Swift, which is an extraembryonic area, produces absence of the germ cells. Chorionic fusion of heterosexual twins causes the masculinized freemartin in cattle and possibly in the pig, but not in the cat, peludo, marmoset or man, showing that such fusion varies in effect in different species. The evolutionary history of the endocrines is just beginning to attract attention but is already of great interest.

Although a very conservative point of view is noted throughout the text, statements which appear distinctly hazardous, occasionally are noted. For example, that attempts to cure sterility by hormone therapy are readily frustrated by the antihormone action set up in the patient. In the opinion of the reviewer, many other factors might account for ill success. The surmise that the normal rate of the human ovarian production of estrogens is 500,000 International Units per day is not borne out by the many blood bio-assays so far described in the nonpregnant. No more than 25 to 35 units of estrogenic activity have ever been demonstrated. A very conservative standpoint is well demonstrated by the fact that the placenta is only considered as a *possible* endocrine gland (the italics are mine). . . . "The evidence is strong but falls short of rigid proof."

While the major portion of the book will be of interest chiefly to the laboratory investigator, the concluding section contains such clinically important subjects as the relation of vitamins to the sex glands; the sex drive and sex function in man. This last chapter can be read with profit particularly by the over-optimistic endocrinologists who will find that although the results of therapy are of extreme importance, up-to-date, negative results far overshadow positive achievements.

—R. T. Frank.

August Mayer has written a short monograph on the *Constitution in Obstetrics and Gynecology*.<sup>22</sup> This interesting sketch takes up normal and abnormal constitution, particularly the physical and psychologic sex differences. Body types versus disposition to diseases are described. Considerable importance is attached to the development of the teeth and palate. A detailed description of the effects of infantilism, particularly on the genital tract, is given. Included are other characters of this group such as the physical and mental, the frequency of dysmenorrhea, susceptibility to myoma and cancer. Many of the illustrations are borrowed from Stratz, Sellheim, and other classic sources.

—R. T. Frank.

### Miscellaneous

*Problems of Ageing*<sup>23</sup> is a symposium under the editorship of E. V. Cowdry, sponsored by the Josiah Macy, Jr., Foundation, and likewise indirectly by the Union of American Biological Societies and the National Research Council. There are twenty-six contributors, well known in their line. The book is 758 pages in length and covers the subject as adequately as the present state of our knowledge permits.

The contents is extremely fascinating, beginning as it does with the aging of plants, covering the senescence and death in protozoa and invertebrates, the ageing of insects, and of vertebrates. It then takes up human cultural levels, including anthropometry of old age, length of life, age differences in illiterate societies, attitude toward the aged, and similar subjects. Longevity, in the past and future, based on statistical tables is discussed.

Next the effect of age on the various organ systems is dealt with. Best known appeared to be the cardiovascular, digestive, skeletal and locomotor, as well as the

<sup>22</sup>*Die Konstitution in der Geburtshilfe und Gynaekologie.* Von Professor Dr. August Mayer, Direktor der Universitäts-Frauenklinik in Tübingen. With 42 illustrations. 57 pages. Verlag von Ferdinand Enke, Stuttgart, 1938.

<sup>23</sup>*Problems of Ageing. Biological and Medical Aspects.* Edited by E. V. Cowdry. Washington University in St. Louis. 121 illustrations, 758 pages. Williams & Wilkins Company, Baltimore, 1939.

Several years ago the late Professor Sedgwick complained that unfortunately the obstetrician is inclined to look upon the newborn infant as an inevitable by-product of his successful effort to separate the fetus from the mother. Conditions have changed since then. In most obstetric departments and maternity hospitals the newborn ward now is more or less under the control of the pediatric staff. Text-books of obstetrics devote an ever increasing amount of space to the consideration of the physiology and pathology of the newborn.

For some time a short elective course has been offered to the seniors in the Johns Hopkins Medical School. The material covered in these special lectures, in amplified form, has been presented by Emerson L. Stone in a little volume, entitled *The New-Born Infant. A Manual of Obstetrical Pediatrics*,<sup>19</sup> now published in a second, revised edition. However, this subtitle does not fully reveal the sum total of useful information it contains.

The author discusses thoroughly, from the viewpoints of prevention, diagnosis, and treatment, not only care and feeding of the well or sick infant but also deals competently with specific problems of interest among others to the dermatologist, neurologist, internist, or orthopedic surgeon.

—Hugo Ehrenfest.

### Endocrinology

In 1936 Van Dyke published *The Physiology and Pharmacology of the Pituitary Body*. He now adds Volume II<sup>20</sup> which is a critical digest of the experimental and clinical literature on the pituitary body that has appeared from 1935 to 1937, with some reports of 1938. The bibliography covers 1,418 titles.

The main subjects dealt with are the anatomy of the pituitary; regulation of growth by the pituitary body; gonadotropic hormones including those in pregnancy and neoplasms; the lactogenic hormone and thyrotropic hormone; the various relationships between the anterior pituitary and the adrenals; the effects on metabolism, and the effect on chromatophores and pigmentation.

The author has changed his opinion and now believes that the posterior lobe is an important gland of internal secretion, with particular effect on water metabolism. This digest is a valuable contribution.

—R. T. Frank.

The second edition of *Sex and Internal Secretions*<sup>21</sup> under the editorship of Edgar Allen is, as before, a cooperative survey of advances in researches of internal secretion in relation to sex. As in the previous edition, the Committee for Research in problems of sex of the National Research Council, has aided with its support. This 1,346 page volume is encyclopedic in scope and will prove a valuable source book for those interested in laboratory research. The book is divided into five sections, covering the biologic basis of sex; the physiology of the sex glands, germ cells and accessory organs; biochemistry and assay of gonadal hormones; the hypophysis and the gonadotropic hormones of blood and urine in relation to the reproductive system; and additional factors in sex functions and endocrine applications in man. Twenty-seven contributors have covered this immense field.

In spite of the many contributors, the text, on the whole, is even, and few repetitions or contradictions are noted. The main interest has been focused to give a broad and yet detailed outline of the bewildering number of individual researches found in the literature, and by means of this, to give as complete a picture as the present state of our knowledge will permit. In this, the authors have been, on the

<sup>19</sup>*The New-Born Infant. A Manual of Obstetrical Pediatrics.* By Emerson L. Stone, M.D., Associate Clinical Professor of Obstetrics and Gynecology, School of Medicine, Yale University, etc. Second edition, thoroughly revised, 291 pages. Lea & Febiger, Philadelphia, 1938.

<sup>20</sup>*Physiology and Pharmacology of the Pituitary Body. Volume II.* By H. B. Van Dyke, Head of Division of Pharmacology, Squibb's Institute for Medical Research, etc. Illustrated, 402 pages. University of Chicago Press, Chicago, 1939.

<sup>21</sup>*Sex and Internal Secretions. A Survey of Recent Research.* Editors: Edgar Allen, Yale University; Charles H. Danforth, Stanford University; and Edward A. Doisy, St. Louis University, with foreword by Robert M. Yerkes, Yale University. Second edition, illustrated, 1346 pages. Williams and Wilkins Company, Baltimore, 1939.

postoperative radiation. The various operative methods and anatomic relations underlying them are fully illustrated together with the indication and selection for the various types of operation.

In the next part of the book, he proceeds to the subject of constitutional treatments which here, probably for the first time, has been given special consideration. He discusses the psychology of the cancer case, hygiene and diet, the literature on the composition of diets which will influence the regression of cancer. He further, under constitutional treatment, discusses the value of chemotherapy, with the proposed effects that certain biologic products and chemicals may exert upon cancer cells. He states in regard to lead, which at one time was proposed in the treatment of cancer of the breast and uterus, that its usefulness has been greatly overestimated, and the enthusiasm for its use had reached far beyond its possibility for cure. He devotes sixteen pages to the present aspects of organotherapy, but concludes that experimental evidence seems to indicate that "endocrines" are not of any value in treatment. The subject of irradiation by both x-ray and radium is voluminously considered from every possible angle; dosage, technique, results, use in metastases, use in multiple tumors, and so forth. Behan calls attention to the fact that the cancer of the breast patient from time to time should be released from treatment in order to build up his psychology and mental reserve.

While the context of the book is based upon the problem of cancer of the breast, the comprehensiveness of the general problems, the wise evaluation of theories and methods of treatment, and the extensive documentation should make this a book of unusual value.

—Philip F. Williams.

*Handbook on Cancer*<sup>25</sup> was prepared by the Committee on Cancer Control of the Canadian Medical Association for the general practitioner. It is elementary but informative, dealing with the recognition and treatment of cancer in all the organ systems. It is sufficiently detailed to be of real use as a primary source book for the practitioner.

—R. T. Frank.

The second edition of Cole and Elman, *Textbook of General Surgery*,<sup>26</sup> as previously, is designed for practitioners and medical students. It is largely based on the third year course for medical students at Washington University. The book has evidently filled a real demand because the second edition follows three years after the first. Because of this, no change in the paging has been attempted but by means of judicious deletion and printing in small type, such new subjects as sulfanilamide, vitamin K in bleeding of jaundice, decompression of the intestinal tract in obstruction, the histamine glare test to determine level of amputations, and the more conservative attitude toward pancreatic necrosis have been included. The book is over a thousand pages in length, and contains 559 illustrations. It is well written, comprehensive and up to date. Each chapter has its short bibliography and there is even an authors' index. The book seems to fulfill its purpose most adequately.

—R. T. Frank.

As indicated in its title, *The Fundamentals of Internal Medicine*,<sup>27</sup> this volume, written by many collaborators and edited by Wallace Mason Yater, is designed primarily for the student. As stated in the Preface this work is intended to provide

<sup>25</sup>*Handbook on Cancer*, for the medical profession. The Authorship Committee, Department of Cancer Control, Canadian Medical Association, Toronto, 1938.

<sup>26</sup>*Textbook of General Surgery*. By Warren H. Cole, Professor of Surgery, University of Illinois, College of Medicine, etc., and Robert Elman, Associate Professor of Surgery, Washington University School of Medicine, St. Louis. Second edition, 559 illustrations, 1031 pages. D. Appleton-Century Company, New York, 1939.

<sup>27</sup>*The Fundamentals of Internal Medicine*. By Wallace Mason Yater, Professor of Medicine and Director of the Department of Medicine, Georgetown University School of Medicine, etc. First edition, with 255 illustrations, 1021 pages. D. Appleton-Century Company, Inc., New York, 1938.

effect of age on the skin. The effect of age on the endocrine glands, including the sex glands, the effect of age on personality and psychosexual phenomena, aging of the nervous system and the special senses, are all included.

The psychologic aspects of aging, the changes in the chemical, and homeostatic mechanisms, the body fluids, and tissue susceptibility, are discussed. Finally, aging from the viewpoint of the clinician concludes this very careful study.

One gathers that as the proportion of older individuals in the population increases, the medical and social importance of age becomes more and more important. The biologic consideration of growth, development, maturation and senescence in all living organisms has been considered from two viewpoints, the one, the inevitable involution, the other, the effect of outside influences, such as infection, trauma, etc., that is, the effect of various environments upon aging. Differently put, it includes normal senescence versus the pathology of old age. The object is not only the conservation of life, but the increase of well being in older individuals.

The world at present is confronted with a declining total population and an increase in the older members of its constituents. In this mechanical age, there is a premium on youthful vigor with a great discount on experience which shows itself in a restriction of child labor and the strong movement for old age pensions. As experience is considered of such little value, particularly in industry, it is important to try to develop activities in which the aging group can engage with most satisfaction to themselves and most benefit to the community. John Dewey says that the many perplexing problems which now attend human old age have an important psychologic-social origin.

—R. T. Frank.

Dr. Behan began this volume on *Cancer*<sup>24</sup> as a treatise on cancer of the breast. In order to elucidate the problems of that condition he found it necessary to incorporate a comprehensive discussion of the biologic history of malignancy with the result that his effort gives us a splendid consideration of the subject of malignancy. The book should be of tremendous value to anyone who is not intimately concerned in the work of the general cancer clinic, and even to such workers the detailed documentation will make the book an exceedingly valuable reference volume and source of bibliography.

There are thirty-nine chapters in the text. It begins with a general consideration of cancer which he classes as a "biological variation in which the cells have acquired a high power of development of multiplication but have lost the power of contact." The statistical analyses show the importance of the cancer problem. It is stated that in twenty years the incidence of cancer of the breast in women of the United States increased 50 per cent. Such relationships as nutrition, race, sex, age, and the like are brought out. The etiologic factors are discussed from the standpoint of systemic organs, heredity, familial disposition, immunity against cancer, and the dysfunctions of the endocrine glands. The relationship between ovarian dysfunction and cancer of the breast is considered at length, and should be of interest to gynecologists and obstetricians. Behan states that there is a considerable doubt whether chronic irritation alone is sufficient in the absence of any inherent cell defect or inherited tendency to cause a malignant growth. He feels that both the benign and malignant processes are probably produced by the same initial underlying causative statement.

Pathology and pathologic physiology of cancer of the breast are fully taken up. Clinical aspects of symptoms and subjective signs are presented in a thorough fashion. The author devotes a long chapter to noncancerous tumors of the breast, then proceeds to diagnosis and diagnostic tests, following which he considers metastases developing in the course of the mammary carcinoma. He discusses the statistics regarding prognosis, which throw light on the various factors which may influence life expectancy in this condition. Behan discusses the various methods of operative and nonoperative treatment and a detailed presentation on pre- and

<sup>24</sup>*Cancer*, with special reference to Cancer of the Breast. By R. J. Behan, M.D., F.A.C.S., Cofounder and Formerly Director of the Cancer Department of the Pittsburgh Skin and Cancer Foundation. Illustrated, 844 pages. The C. V. Mosby Company, St. Louis, 1938.

*Landmarks in Medicine*<sup>30</sup> are seven lectures delivered to the laity under the auspices of the New York Academy of Medicine. The subjects dealt with are the history of medicine, the development of research, the progress in x-ray, the subject of longevity, and the activities of the medical examiner featuring the improvement following the abolishment of the antiquated coroner's system. These lectures are readily understood and informative, having been delivered by well-known specialists in each field.

—R. T. Frank.

*Clinical Laboratory Methods and Diagnosis*<sup>31</sup> after only three years appears in a second edition. This volume of over 1,600 pages covers every phase of laboratory diagnosis. In the new edition all of the recent advances have been incorporated. This applies particularly to the newer conceptions on nephritis and nephrosis, the expansion of the chapter on hematology, as well as that on parasitology and tropical medicine.

All the various laboratory methods of diagnosis are dealt with, including bacteriology, serology, post-mortem examination and toxicology. This is a very complete exposition of the subject which should be of great use to all engaged in laboratory work. The subject matter is so large that it does not lend itself to detailed review.

—R. T. Frank.

*The Genuine Works of Hippocrates*<sup>32</sup> translated from the Greek by Francis Adams LL.D., Surgeon, is a reprint reproducing the first English translation of 1849 of Francis Adams, a Scottish surgeon. In this edition, no footnotes are appended. Those interested in medical history will find it pleasant reading.

—R. T. Frank.

*Alcohol in Moderation and Excess* by Waddell and Haag<sup>33</sup> was primarily written for the school system of the state of Virginia. It was designed to be used as a source book for teachers in instruction in physiology and hygiene, on account of the law of Virginia which made it mandatory to give, in the courses in physiology and hygiene, a view of the evil effects of alcohol and other narcotics on the human system. The book, in spite of its excellence and objectivity, was rejected by the legislature. It contains much of interest, including the effect of alcohol on auto accidents, insanity; the food value of alcohol; its effect on basal metabolism and other physiologic bi-effects.

—R. T. Frank.

*Consultation Room*<sup>34</sup> by Frederic Loomis of Oakland, California, is a selection of episodes and anecdotes from twenty years of the author's medical life in which he has "selected problems of human lives and human relations, counterparts of which are factors in the interesting but perplexing life of every physician."

These autobiographic sketches of a gynecologist and obstetrician contain crisp and attractive episodes beginning with his early life, his start in medical school, through his internship, and later activities in practice. Apparently selected at random, it will be found that each has its reason and that the whole illuminates many phases which rarely are enlighteningly touched upon and described for the laity. The style is interesting, the anecdotes amusing, some of the episodes touching and showing the trials and temptations to which a physician is subjected, as well as the difficulties encountered in treating his patients intelligently and fairly.

—R. T. Frank.

<sup>30</sup>*Landmarks in Medicine.* Laity Lectures of the New York Academy of Medicine. Introduction by James Alexander Miller, M.D., President of the Academy. D. Appleton-Century Company, New York, 1939.

<sup>31</sup>*Clinical Laboratory Methods and Diagnosis.* A Textbook of Laboratory Procedures with Their Interpretation. By R. B. H. Gradwohl, M.D., Director of the Gradwohl Laboratories, etc. Second edition, with 492 illustrations in the text and 44 color plates, 1607 pages. The C. V. Mosby Company, St. Louis, 1938.

<sup>32</sup>*The Genuine Works of Hippocrates.* Translated from the Greek by Francis Adams, LL.D., Surgeon. The Williams & Wilkins Company, Baltimore, 1939.

<sup>33</sup>*Alcohol in Moderation and Excess.* By J. A. Waddell, M.D., Professor of Pharmacology, Materia Medica and Toxicology, Medical Department, University of Virginia, and H. B. Haag, M.D., Professor of Pharmacology, Medical College of Virginia. William Byrd Press, Inc., Richmond, Va., 1938.

<sup>34</sup>*Consultation Room.* By Frederic Loomis, M.D. Alfred A. Knopf Inc., New York, 1939.

the foundation upon which the superstructure of more detailed and extensive knowledge may be built. In concise and systematic arrangement that "minimum amount" of information is presented, which "a student or general practitioner should have at his fingertips." Outstanding features of this book are the well-selected illustrations, many instructive tables, mostly referring to essential points in differential diagnosis, and its final section (XXI) dealing with diet in general and specific diets in various diseases.

—Hugo Ehrenfest.

The second edition of Meakins, *The Practice of Medicine*,<sup>28</sup> is a volume of more than 1,400 pages which has brought this book fully up to date. It is a pleasure to encounter a vividly written, a well and profusely illustrated textbook of medicine. The illustrations add greatly to the value of the text, are 521 in number, including many colored plates, and cover x-rays, electrocardiograms, charts, and graphs, in addition to the depiction of such lesions which lend themselves to photography as well as many sections and microphotographs of organs. Symptomatology is stressed but laboratory aids are not undervalued. The book is designed for the student and practitioner. It covers every phase of internal medicine. Certain chapters have been written by other authors: the nervous system by Petersen, the urinary by Sriver, the metabolic disorders and glands of internal secretion by Mason.

This is a very excellent textbook which covers the field most adequately and is designed for quick reference as well as continuous reading.

—R. T. Frank.

The customary strict division between the profession of medicine and dentistry admittedly has delayed adequate appreciation of the rôle played by dental pathology in the causation of various diseases. The medical student, in the interest of public health, must become familiar at least with the basic facts of modern dental science. From this viewpoint McCall's small volume, dealing with the *Fundamentals of Dentistry in Medicine and Public Health*,<sup>29</sup> can be said to fill a long felt want.

The obstetrician necessarily is interested in the intimate dental and systemic interrelations in two respects: The possible effect of infected mouth or teeth on the health of the pregnant woman and the preservation of teeth already deciduous during pregnancy. The significance of dental focal infection in the origin of certain types of toxemia is generally appreciated.

In the author's belief proper attention consists in a combination of expert dental care with a dietetic regime that will guarantee adequate food intake containing both quantitative needs and the proper proportion of essentials. The mineral metabolism in this respect is of greatest importance.

It seems noteworthy that the author, a dental specialist, does not mention oral administration of calcium. Many obstetricians routinely advise this medication which actually is indicated and justified only under certain conditions. A Report of the Council of Pharmaceutics of the American Dental Association (1936) contains the definite statement: "The evidence in favor of administration of calcium compounds (during pregnancy) is not of such nature as to warrant the claims that supplies of calcium or of phosphorus supplemental to that obtained by diet are necessary." Recent obstetric literature strongly suggests that an excess of calcium intake might induce abnormal ossification of skull bones or lead to noxious calcification of the placenta.

Careful perusal of this book must be recommended to all practitioners, especially to those interested in obstetrics.

—Hugo Ehrenfest.

<sup>28</sup>*The Practice of Medicine*. By Jonathan Campbell Meakins, M.D., Professor of Medicine and Director of the Department of Medicine, McGill University, etc. Second edition, with 521 illustrations including 43 in color. The C. V. Mosby Company, St. Louis, 1938.

<sup>29</sup>*Fundamentals of Dentistry in Medicine and Public Health*. By John Oppie McCall, Director of the Murry & Leonie Guggenheim Dental Clinic, New York, etc. 50 illustrations, 161 pages. The Macmillan Co., New York, 1938.

# Department of Reviews and Abstracts

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CONDUCTED BY HUGO EHRENFEST, M.D.

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## Selected Abstracts

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### Pregnancy and Disease

Reid and Mackintosh: Incidence of Anemia in Pregnancy: Influence of Social Circumstances and Other Factors, *Lancet* 1: 43, 1937.

The hemoglobin level was estimated in 1,108 pregnant women; 10.2 per cent gave a reading below 70 per cent. The anemia was always hypochromic. When the women were divided into two groups according to the family income, it was found that the incidence of anemia was higher in the lower income group. Multiparity in women in good social circumstances did not appear to have much influence, except in women with five or more pregnancies. Age, work outside the home, or abnormality in pregnancy had no recognizable influence on the degree of anemia.

J. P. GREENHILL.

Naish, F. C.: A Study of the Immediate and Remote Effects of Pregnancy on Diseases of the Heart, *J. Obst. & Gynaec. Brit. Emp.* 44: 659, 1937.

A study of 63 patients during 83 pregnancies over a period of eleven years suggests that pregnancy and its accompanying problems impose a burden upon the damaged heart which leads to permanent crippling. On the other hand, it is likely that the damaged heart would deteriorate during eleven years even in the absence of childbearing, but it has been found impossible to obtain nulliparous control cases. The damage is increased when the pregnancies become multiple. Too frequent pregnancies put more strain on the heart than those more widely spaced.

Syncope is a symptom which indicates a guarded prognosis in cases of aortic reflux. Patients suffering from aortic stenosis do not tolerate pregnancy well. Auricular fibrillation is rare and does not occur at an early age; nevertheless it occurs at an earlier age in parous than in nulliparous women. The prognosis is poor in all cases.

Complete heart block may not be a contraindication to pregnancy. Cases of bundle branch block have a poor prognosis. Hemoptysis is always a sign of congestive failure. Extrasystoles indicate an increased irritability of the affected part, but are common in normal pregnancy. In cases of mitral stenosis auricular extrasystoles may be precursors of auricular fibrillation.

A follow-up of 22 per cent of the patients showed 37 per cent worse than before their pregnancies. The patients in whom the heart was decompensated during pregnancy showed the greatest degree of permanent crippling afterwards. In the opinion of the author antenatal rest for therapeutic and routine purposes is of great value. The question of anesthesia requires consideration of the type of heart disease, the procedure for which the anesthetic is required, and the experience of the anesthetist.

J. P. GREENHILL.

# Society Transactions

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## OBSTETRICAL SOCIETY OF PHILADELPHIA

*MEETING OF MARCH 2, 1939*

The program was as follows:

**Herniation of Amniotic Sac Into the Subcutaneous Tissues in a Pregnancy Following Cesarean Section.** Dr. Franklin M. Kern.

**Nephrectomy During Pregnancy.** Dr. George L. Hoffman. (For original article, see page 514.)

**Studies on the Concentrations of Estrogenic and Gonadotropic Hormones in the Serum of Pregnant Women.** Dr. A. E. Rakoff (by invitation). (For original article, see page 371.)

**Some Summaries in the Technique of Hysterectomy.** Dr. E. G. Maier.

**X-ray Localization of the Placenta by Soft Tissue Technique and Without the Use of Opaque Media.** Dr. R. M. Smith.

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## CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF MARCH 17, 1939*

The following papers and discussions were presented:

**Surgical Treatment of Bilateral Polycystic Ovaries—Amenorrhea and Sterility.** Drs. Irving F. Stein and Melvin R. Cohen. (For original article, see page 465.)

**Treatment of the Menopause With Estradiol Dipropionate.** Drs. Edward M. Dorr and R. R. Greene. (For original article, see page 458.)

**The Complications Associated With Excessive Development of the Human Fetus.** Drs. Arthur K. Koff and E. L. Potter (by invitation). (For original article, see page 412.)

*(Note: The Transactions of the February meeting will appear in a subsequent issue.)*



During the first twelve to sixteen weeks of pregnancy, therapeutic abortion is indicated in all proved active cases of pulmonary tuberculosis. This holds true for any stage of pulmonary tuberculosis, early or late.

From the sixteenth to the twenty-eighth week, artificial interruption should rarely be undertaken, except in active cases in which the patients are growing rapidly worse.

From the twenty-eighth to the fortieth week, nothing can be done that will improve the condition. "Watchful waiting" may seem cowardly, but surgical intervention is almost sure to terminate fatally.

If the pregnancy has been carried to or near full term, labor should be made as easy and short as possible. As soon as the cervix is fully dilated rupture of the membranes, if these have not previously ruptured, episiotomy with application of forceps and immediate delivery using gas-oxygen, cyclopropane or local anesthesia during the active delivery is the procedure of choice.

J. P. GREENHILL.

Seadding, J. G.: *Pregnancy and Oleothorax*, *Lancet* 1: 1329, 1938.

The author reports a case of tuberculosis treated by oleothorax because of an adhesive pleuritis developing subsequent to artificial pneumothorax performed four weeks post partum.

The course of a second pregnancy beginning two months following oleothorax was uneventful. There was no significant interference with the intrapleural pressure.

It is suggested that in suitable cases this method of collapse therapy should be considered.

CARL P. HUBER.

White, G. M., and Porter, D. F.: *Miliary Tuberculosis in a Newborn Infant*, *Canad. M. A. J.* 39: 165, 1938.

The authors report the case of an infant who died of miliary tuberculosis on the forty-sixth day of life. Evidence of the infection was noted during the first week of life. No postnatal contact could be determined though all those in contact with the infant were investigated clinically and roentgenologically. The father showed no evidence of tuberculosis. The mother showed evidence of a childhood tuberculosis without activity and a normal course ante partum and post partum. The possibility of placental transmission of the disease during the last weeks of gestation is discussed. The placenta was not examined.

CARL P. HUBER.

Zakon, S. J.: *Prenatal Syphilis a Preventable Disease*, *Illinois M. J.* 71: 438, 1937.

The author states that every woman who has syphilis is in a contagious and infectious stage throughout her childbearing period, regardless of the fact that clinically the case may be classified as latent. The transmission of syphilis from the mother to the fetus takes place about the fourth month of pregnancy. Pregnancy occurring during late syphilis may or may not terminate with fetal infection. The prevention of prenatal syphilis is simple, and under favorable conditions almost certain. Zakon urges early prenatal care with serologic tests regardless of the social status of the expectant mother. Bismuth is used exclusively in the treatment of syphilis during the period of gestation. In a series of 116 carefully followed-up patients who were treated during pregnancy, 107 children were born serologically negative. Nine children were born serologically positive to 9 mothers receiving antisyphilitic treatment, but only one as early as the fourth month of pregnancy.

EUGENE AUER.

Schultz, W.: Prognosis and Treatment of Circulatory Disease in Pregnancy, Arch. f. Gynäk. 166: 62, 1938.

The author divides all cardiac disease into three groups determined by compensation, latent decompensation and decompensation. His experiences lead him to conclude that there is no indication to interrupt pregnancy with full compensation. Latent decompensation is an indication for interruption. Decompensation is also an indication but the interruption must never be done during the state of decompensation and must await the re-establishment of complete cardiac compensation. The author feels that pregnancy is interrupted much too frequently, and that pregnancy, labor, and the puerperium are usually less of a strain on the cardiac patient than is the added work of caring for the newborn baby. This feature of proper care of the cardiac patient is all too frequently neglected.

RALPH A. REIS.

Danforth, W. C.: The Management of Pregnancy and Labor in the Presence of Heart Disease, Illinois M. J. 74: 88, 1938.

Danforth states that the woman with a murmur, whose heart is perfectly compensated, will probably go through pregnancy and labor without trouble. If perfect compensation is present no treatment is needed except to caution the patient against undue exertion, for normal pregnancy alone causes a 50 per cent increase in the work done by the heart. Decompensation in the first trimester of pregnancy demands termination of the pregnancy. Danforth does not believe in premature induction of labor in cardiac cases as this type of labor is frequently unsatisfactory. Morphine and ether are the analgesics of choice. Labor should proceed normally until dilatation becomes complete. Forceps delivery should replace all of the second stage which is not accomplished by the unaided force of the uterine contractions, for no voluntary effort should be allowed. Cesarean section should be used only rarely.

EUGENE S. AUER.

Matthews, H. B.: Pregnancy and Tuberculosis, Am. J. Surg. 35: 293, 1937.

What is to be done to insure adequate care, both medical and obstetric, for the pregnant tuberculous woman? Matthews offers the following suggestions:

1. The ideal set-up for a tuberculosis and pregnancy clinic would be a special institution devoted exclusively to care and treatment of pregnant tuberculous women. Here would be working in close harmonious cooperation a specialist in tuberculosis, an expert obstetrician interested in tuberculosis, a pediatrician interested in tuberculosis, a roentgenologist and the whole group supported by good pathologic and bacteriologic laboratories.

2. In lieu of this ideal set-up, it is proposed that the hospital allocate a certain number of beds for pregnant tuberculous women and that these patients be under the direct supervision of a tuberculosis specialist in cooperation with an obstetric specialist. After the seventh month of pregnancy the obstetrician should assume first control of the patient, with the tuberculosis specialist cooperating. The obstetrician is to continue in charge until after the postpartum period (two or three weeks or longer), following which the tuberculosis specialist again assumes charge and manages the case as he would any other case of tuberculosis.

Management of the baby should be put under direct supervision of a pediatrician interested in tuberculosis as soon as the umbilical cord is ligated. The baby should never be allowed to nurse, except perhaps in cases in which the mother has a minimal, healed lesion, and it is highly desirable to give the baby a good start in life. In such cases the baby may be nursed for six to eight weeks.

and also the pressure caused by the gravid uterus, the author believes that the hematuria was either the result of a toxic factor of pregnancy or due to a dilating effect of pregnancy hormones on the renal capillaries.

AUGUST F. DARO.

**Turley, H. K.:** Management of Pyelitis of Pregnancy, *South. M. J.* 31: 729, 1938.

The mechanical obstruction of the ureter at the pelvic brim by the enlarging uterus with subsequent proximal dilatation and stasis, producing what has been termed a "physiologic hydronephrosis," is generally accepted as the causal factor. The condition occurs with greater frequency on the right side, and usually makes its clinical appearance about the sixth month, although ureteral dilatation begins early in gestation. Stasis in the urinary tract favors infection. Distant foci may be predisposing factors, and the route of infection may be either by the lymphatics or the blood stream. The organisms most frequently present are *B. coli*, staphylococci and streptococci. Intravenous urography is a most useful method of investigating the presence of urinary tract anomalies, the size and position of the kidney and ureters.

Pyelitis in early pregnancy can be cured. In the latter half of gestation only control of the infection may be expected. Urologic investigation should be performed when pyelitis develops in the first trimester before the uterus has attained sufficient size to cause obstruction, in order to rule out the presence of anomalies that may have antedated the gestation. In acute cases fluids should be forced and the patient alkalinized. Should no improvement occur in 24 to 36 hours, ureteral catheterization is indicated with fluid administration by intravenous route (3,000 to 4,000 c.c. of 5 per cent glucose) and by mouth. When the temperature is normal the catheters should be removed and urinary antiseptics or acidifying agents given. Methenamine, ammonium chloride and mandelic acid are useful preparations. A ketogenic diet is contraindicated. One should watch for symptoms of acidosis. Lavage of the renal pelvis at ten-day intervals is indicated upon failure of response to the urinary antiseptics or the acidifying agents.

After the fifth month of pregnancy treatment should be directed toward controlling the infection until after the delivery, rather than an attempt at a cure. Resort may be had to ureteral catheterization in patients with chills, fever and sweats who have not responded to the more conservative regime of diuresis and alkalization. Since ureteral catheters are of value only while they are in place, and should be left in situ not more than 36 to 72 hours, it is advisable to employ postural drainage. With the patient in dorsal position, and the foot of the bed elevated 12 to 14 inches, there is an upward displacement of the kidney which tends to stretch kinked ureters and effects some release of uterine pressure on the ureters at the pelvic brim. When pain and toxic symptoms have disappeared, the patient is advised to rest two hours daily in this position and sleep at night with the foot end of the bed raised.

The severe secondary anemias which tend to develop in severe febrile attacks of pyelitis should be watched for and treated by blood transfusions.

Where response to treatment fails, and there is no abatement of toxic symptoms, interruption of pregnancy is advised. Kidney surgery carries great risk and is rarely indicated.

ARNOLD GOLDBERGER.

**Gibson, A. J.:** Twin Pregnancy Complicated by Bilateral Hydronephrosis, *Med. J. Australia* 1: 472, 1937.

Because of hematuria, frequency of urination, headaches, edema, and slight albuminuria developing at the thirty-sixth week of gestation in a 29-year-old multipara with twin pregnancy, an intravenous pyelogram was done to rule out gross renal abnormality. An advanced degree of bilateral hydronephrosis was detected.

Smyth, Francis Scott, and Olney, Mary B.: *Diabetes and Pregnancy*, J. Pediat. 13: 772, 1938.

Personal studies together with critical consideration of the literature lead the writers to conclude that under rigid control, pregnancy in a diabetic woman may take a satisfactory course and yield a normal child. It is difficult to prove that the infantile insulin production has any effect on the maternal blood sugar. When the maternal diabetes has not been adequately controlled, the newborn infant may present temporary symptoms referable to hypoglycemia, which may persist up to three weeks and may require parenteral glucose administration. In some instances the hypoglycemia seemed to be correlated to a hypertrophy or hyperplasia of the Langerhans Islets as ascertained at necropsy. Relative macrosomia, advanced bone age, and a more mature genital tract suggest a pituitary effect. With further advance of information on endocrine relationships, it might become possible to account for mild as well as the fatal hypoglycemia of the newborn. Fetal glycogen storage hypertrophy is postulated by the writers as possible etiology for some of the pathology found post mortem.

HUGO EHRENFEST.

Hector, A. G., and Giove, J. L.: *Spontaneous Glycosuria During Pregnancy and the Puerperium*, Bol. Soc. chilena de obst. y ginec. 3: 367, 1938.

From an extensive study the authors conclude that glycosuria is not very frequent in pregnancy. It was found in only 2.85 per cent of the cases observed, occurring generally in the middle third of pregnancy. It was present more frequently in multiparas than in primiparas. A low renal threshold for glucose appears with pregnancy and disappears with parturition.

Lactosuria during pregnancy is very rare and occasionally may follow glycosuria but is absolutely independent. Lactosuria in the puerperium is more frequent. The authors found it in 69 out of 100 cases. It is very transitory, disappearing usually from ten to twelve days after the child is born.

MARIO A. CASTALLO.

Gray, C. H.: *Ketonemia in Diabetes and Pregnancy*, Lancet 2: 665, 1938.

In the diabetic patient a close agreement was found between the degree of ketonemia and ketonuria as well as with the clinical condition. In pregnancy 1 per cent of 3,000 patients showed a positive Rothera test for ketone bodies in the urine. Blood ketones varied within normal limits even in 5 cases of eclampsia. There is a greater lability to ketosis in pregnancy as shown by 17 positive Rothera tests in 27 pregnant patients following a fourteen-hour fast as compared with no positive tests in 27 nonpregnant patients.

CARL P. HUBER.

Mortara, F.: *Experimental Research on the Functional Alteration in the Number of Functioning Glomeruli During Pregnancy*, Monit. Ostet. ginec. 8: 487, 1936.

From experimental studies on laboratory animals the author came to the conclusion that the number of functioning glomeruli ordinarily represent 38 per cent of the kidney substance, but that during pregnancy this amount is increased to between 55 per cent and 60 per cent.

MARIO A. CASTALLO.

Tamburell, G.: *An Unusual Case of Hematuria in Pregnancy*, Trans. Sicilian Soc. Gynec. & Obst., Meeting of May 14, 1937.

The author describes a case of bilateral renal hematuria recurring in five pregnancies. After having excluded, by history, clinical and laboratory examination, the possibility of a previous kidney disease, tubercular lesion, calculi, renal ptosis,

Garcia, Eusebio Y.: Can Malaria Be Contracted in Utero? J. Philippine Islands M. A. 18: 141, 1938.

The author reports two cases of possible congenital malarial infection with the finding of parasites in the cord in both, and in the internal organs of one of the fetuses whose mother died of cerebral malaria due to *P. falciparum*. He feels that in these two cases he furnished more positive evidence for the possibility of congenital infection with malaria than has so far been recorded in literature by other authors. The possible mechanism of the invasion of the fetal circulation by the parasites from the maternal side is described.

C. O. MALAND.

Hildebrandt, Alwin, and Otto, Hans: Polyneuritis of Pregnancy and Its Response to Vitamin B<sub>1</sub>, München. med. Wchuschr. 85: 1619, 1938.

The authors report the case of a pregnant patient who was severely afflicted with a polyneuritis and to whom was given a total of 1782 mg. of vitamin B<sub>1</sub> besides other vitamins, during the entire period of pregnancy, with no untoward symptoms of overdosage or of any cumulative effects. A healthy child was normally born and the polyneuritis was cured. A number of laboratory studies showed that until shortly before delivery no vitamin B<sub>1</sub> was excreted and vitamin C in only a small quantity; but at the time of and after delivery a normal output was observed in the urine and vitamin B<sub>1</sub> could be found in the serum. Along with the improvement of the polyneuritis under the treatment with vitamin B<sub>1</sub>, the subacidity of the gastric juice became normal, and the existing hypochromic anemia was cured, the blood sugar was slightly affected (temporarily lowered), and an existing liver disturbance was adjusted. Before any interruption of pregnancy is undertaken, despite the severe symptoms of paralysis, a trial with vitamin B<sub>1</sub> is advisable.

C. E. PROSHEK.

(To be continued.)

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## Item

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### American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 6, 1940, at 2:00 P.M. The Board announces that it will hold only one Group B, Part I, examination this year prior to the final general examination (Part II), instead of two as in former years. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held in June, 1940.

*Applications for admission to Group B, Part I, examinations must be on file in the Secretary's office not later than October 4, 1939.*

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J., on June 8, 9, 10, and 11, 1940, immediately prior to the annual meeting of the American Medical Association in New York City.

Applications for admission to Group A, Part II examinations must be on file in the Secretary's office not later than March 15, 1940.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I examinations (written paper and case records) and the Part II examinations (pathological and oral).

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Normal spontaneous birth of twins occurred three weeks before term. Approximately two months post partum the pyelogram was repeated and revealed persisting, definite bilateral dilatation of the calyces and ureters with no evidence of hydro-nephrosis; kidney function fairly satisfactory.

Dilatation of the upper urinary tract which occurs in nearly every pregnant patient is more marked in primigravidas than in multiparas, developing as early as the tenth week. It is at first uniform bilaterally, but by the end of the fourth month becomes greater on the right side because of uterine pressure. Stasis, which is usually coexistent with dilatation, begins early in gestation and becomes maximal at the sixth month, decreasing near term.

The fact that the ureteral dilatation that occurs with large ovarian cysts not associated with pregnancy is much less than that developing in pregnancy, is evidence that a causal factor exists other than pressure alone. The author suggests that the tone of the urinary tract may be influenced by variations in estrin content of the blood during gestation and the puerperium in much the same manner that uterine tonus is affected.

ARNOLD GOLDBERGER.

McGowan, J. M., and Baker, J. O.: The Relation of Pregnancy to Biliary Disease and the Control of the Vomiting of Pregnancy, *Canad. M. A. J.* 39: 133, 1938.

The authors believe that spasm of the second portion of the duodenum is responsible for the production of vomiting in pregnancy. Such duodenal spasm may be produced in the normal individual by the subcutaneous injection of morphine gr.  $\frac{1}{6}$ . It is relieved by inhalation of amyl nitrite and particularly by the sublingual administration of glyceryl trinitrate (nitroglycerin).

X-ray studies of the duodenum in a case of hyperemesis gravidarum demonstrate the duodenal spasm.

Glyceryl trinitrate, gr.  $\frac{1}{400}$  under the tongue after each meal, has given good results in the control of early cases of vomiting of pregnancy. Five patients successfully treated in this way had not responded to other methods.

CARL P. HUBER.

Kent, C.: Fourteen Personal Cases of Acute Yellow Atrophy of the Liver, *Zentralbl. f. Gynäk.* 62: 429, 1938.

The author observed an epidemic of 14 cases of acute yellow atrophy of the liver in Istanbul. Only one patient survived. All the patients were pregnant, all but one were multiparas and all were between 17 and 33 years of age. The early symptoms were not characteristic but appeared to be those of an intestinal intoxication and not those of hyperemesis or a toxemia. In all cases, the liver was found to be diminished in size clinically. In some cases it was reduced to one-third its normal size. Contrary to the belief of older authors, in not a single instance was the so-called pathognomonic presence of leucin and tyrosin crystals detected. All of the patients aborted.

The author emphasizes that there is a vast difference between acute yellow atrophy and the toxemias of pregnancy. The toxemias of pregnancy, hyperemesis and eclampsia affect chiefly primiparas whereas acute yellow atrophy is observed most often in multiparas. Furthermore, in most cases of toxemia the disease disappears after termination of the pregnancy whereas in acute yellow atrophy neither spontaneous expulsion of the fetus nor artificial interruption of the pregnancy has the least effect on the course of the disease. Death of the fetus in utero is unusual in eclampsia but is the rule in acute yellow atrophy.

The Istanbul epidemic of acute yellow atrophy is a unicum in the history of this disease because ordinarily it is a very rare occurrence.

J. P. GREENHILL.

endometrium of the castrated rabbit. This reaction came to be adopted generally as a method of bio-assay for the active principle of the corpus luteum (Corner-Allen rabbit unit).

Despite these significant studies, the pharmaceutical chemists encountered difficulties in preparing an active extract for clinical use due to the low yield of progestin by corpora lutea of various animals. Moderate amounts were found in the corpora lutea of hogs and cattle, but only small amounts occurred in those of the sheep. Pratt, Hamblen, Kamm and McGinty<sup>7</sup> reported also that the corpora lutea of women contained quite small amounts of progestin: they found that an equivalent of 60 to 100 gm. of fresh corpora lutea was necessary for a positive reaction in the immature rabbit. They observed: "A pair of mature hog ovaries contains in the order of magnitude 20 to 30 times as much progestin as the human ovary. According to the determinations, it takes nearly 40 human corpora lutea to yield 1 Rb. U. of progestin." Various possible explanations of these findings were suggested: the low content of progestin in the human being might indicate a greater sensitivity, with the result that a small amount of the hormone is relatively more effective; on the other hand, progestin might not be stored long in the corpus luteum, but rather might be secreted into the circulation as soon as elaborated. The failure, however, of Bloch<sup>8</sup> to find any progestin in 500 c.c. of blood from a pregnant woman, and the inability of Loewe and Voss<sup>9</sup> to detect but small amounts in pooled specimens of urine from women during the progestational phase of the menstrual cycle were opposed to the latter assumption.

Attempts to circumvent the lack of active preparations of progestin by giving gonadotropic substances derived from the urine of pregnancy were unsuccessful. The theoretical basis for this form of therapy was the assumption that these "luteinizing principles" might cause the ovaries of patients in need of progestational effects to form functional corpora lutea and thereby to form their own progestin. Studies at our clinic<sup>10</sup> during the past ten years have convinced us that even the present preparations of gonadotropes will not produce ovulation and the formation of corpora lutea in ovaries not spontaneously capable of performing these functions. There is a possibility, however, that in certain patients whose corpora lutea are functioning at low levels these may be caused to elaborate more progestin by treatment of this sort.

A practical commercial method for the preparation of quantities of the progestational principle adequate for clinical purposes was made possible by the synthesis of progesterone.

Almost simultaneously in 1934 three groups of workers, Butenandt, Westphal and Cobler,<sup>11</sup> Slotta, Rusehig and Blanke,<sup>12</sup> and Allen and Wintersteiner,<sup>13</sup> isolated crystalline progesterone. The same year Butenandt and Westphal<sup>14</sup> synthesized it from stigmasterol, and later Butenandt<sup>15</sup> announced its preparation from pregnandiol.

There seems to be general agreement among experimental workers that synthetic progesterone possesses all the pharmacologic properties exhibited by active extracts of corpora lutea.

Corner and Allen,<sup>16</sup> upon the basis of observations by them and their group<sup>17</sup> upon laboratory animals, drew the following conclusions: "It may be stated that all 4 of the definitely established effects of corpus luteum extracts upon the uterus; namely, progestational proliferation of the endometrium, inhibition of the

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South Atlantic Association of Obstetricians and  
Gynecologists

Annual Meeting

Charleston, S. C., February 10 and 11, 1939

## THE METABOLISM AND UTILIZATION OF PROGESTERONE GIVEN INTRAMUSCULARLY TO WOMEN\*

E. C. HAMBLÉN, M.D., N. B. POWELL, M.D., AND  
W. KENNETH CUYLER, M.A., DURHAM, N. C.

*(From the Endocrine Division of the Department of Obstetrics and Gynecology, Duke University of Medicine and Duke Hospital)*

G YNECOLOGISTS long have felt the need for an active therapeutic agent having the specific endocrine properties attributed to the corpus luteum. Now that synthetic progesterone has been available for approximately four years, it seems advisable to examine certain clinical data which are pertinent to its pharmacology.

### PRELIMINARY CONSIDERATIONS

The early aqueous extracts of corpora lutea had no demonstrable potency. Iscovesco<sup>1</sup> in 1914, however, prepared a lipid extract which he used clinically with some apparent success. Hermann<sup>2</sup> in 1915 probably produced experimentally progestational alterations of the endometrium with one of these lipid extracts, but it is believed generally that he did not recognize these changes. Hisaw and his group<sup>3</sup> in 1928 prepared extracts which definitely contained the active principle of the corpus luteum. The same year Corner<sup>4</sup> confirmed the observations previously made in 1910 by Ancel and Bouin<sup>5</sup> that the characteristic progestational reaction of the uterus of the gravid rabbit was due to the specific action of the corpus luteum. Corner and Allen<sup>6</sup> in 1929, employing a modification of Hermann's technique of extraction, were able to prepare an alcoholic extract of corpora lutea of sows which was capable of inducing a progestational reaction in the

\*Read at the First Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Charleston, S. C., February 10 and 11, 1939.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."



the factors. (3) A failure of excretion is not conclusive evidence that ovarian function is inadequate. (4) The excretion of the pregnandiol-complex is not evidence that an endometrium is undergoing progestational proliferation.

### THE CLINICAL APPROACH

The factual data to be considered in the present report were secured during the course of the diagnosis and treatment of a group of patients with diverse functional irregularities of uterine bleeding. These data will be segregated into two groups: (1) those concerned with evaluation of the endometriotropic effects of progesterone injected intramuscularly, these effects being judged from the study of serial endometrial specimens secured by biopsy (evidences of endometrial utilization); and (2) those dealing with evidences of metabolic alterations of the progesterone injected, these being based upon determinations of urinary titers of sodium pregnandiol glucuronide.

All of these patients received, during the period of observation to be reported, a system of cyclic therapy either with progesterone alone or with estrogens and progesterone combined. The details of this method of treatment have been reported previously by one of us.<sup>25</sup> They will be summarized briefly at this point:

If menorrhagia or metrorrhagia existed, a remission from bleeding was induced, if necessary, by estrogenic therapy or by a thorough curettage. One week after curettage or directly following the cessation of an episode of bleeding, injections of estrogenic substance in daily doses of 10,000 to 20,000 international units were begun and continued for fourteen days. Progesterone in daily doses of 5 to 10 international units was then started and given daily for seven days. In some instances, daily injections of 10,000 international units of estrogens were continued during the time that progesterone was administered. At the conclusion of this treatment, and frequently before all the progesterone had been given, bleeding occurred. This bleeding has been found, as a rule, to be comparable in amount and duration to that experienced by healthy women. No treatments were given during the week set aside for bleeding. Injections of progesterone were discontinued if bleeding started early. One week after the onset of bleeding, treatments were repeated in the same manner. If bleeding still persisted, the injections of estrogens were found to cause it to cease. Some patients were given only progesterone cyclically. This treatment differed from that described only in the fact that no estrogens were employed; the temporal relationship between treatments with progesterone and bleeding remained the same.

During the period of treatment, endometriotropic effects were judged by biopsies of the endometrium taken at the onset of bleeding, but no later than twelve to twenty-four hours from that time, since the processes of tissue-shedding, necrosis and subsequent regeneration confuse the interpretation of tissue secured later in the course of flowing.

In the group of patients, whose urinary titers of sodium pregnandiol glucuronide were investigated, the following routine was followed. The method of quantitation employed was that described by Venning.<sup>23</sup> Twenty-four-hour specimens of urine were used. No specimens were taken during episodes of bleeding. As a rule daily urines were required during the period of injection of both estrogens and progesterone. In some instances specimens were secured only during the time when progesterone was given. Unfortunately, in some instances, co-operation of the patient was not ideal and specimens were missing at times when their contents might have proved significant. In reporting the values obtained from these studies, we have followed the practice of Venning and given the total

action of pituitrin upon the myometrium, inhibition of uterine motility in vivo, and the suppression of menstruation have now been achieved with crystalline progesterone."

The foregoing conclusions, unfortunately, have not been proved for woman. For the most part critical clinical studies have been concerned with investigations of the endometrial responses, as judged from specimens obtained by curettage or biopsy.

Clauberg<sup>18</sup> in 1932 and Kaufmann<sup>19</sup> in 1933 reported that progestational reactions had been produced in the endometria of castrates by the employment of estrogens and of extracts containing progestin. The doses employed by these two workers were similar: Kaufmann, for example, used a total of 42,000 R.U. of estradiol benzoate given over a period of twenty-one days and followed by a total of 35 Rb. U. (Clauberg units) of progestin given over an interval of seven days. Elden,<sup>20</sup> however, repeated the work of Kaufmann and Clauberg. He was unable to produce progestational alterations in the endometria of 5 human castrates by series of injections of estradiol benzoate, averaging 50,000 R.U. given over periods of fifteen days, which were followed by those of progesterone in amounts ranging from 12 to 60 Rb. U. (Corner-Allen units, each of which is usually considered to be equivalent to 2 or 3 Clauberg units) spread over intervals varying from one to six days. Observations similar to those of Elden, but made upon young women with menometrorrhagia associated with estrogenic endometria rather than upon castrates, were reported about the same time from our clinic.<sup>21</sup> It was observed that injections of progesterone, alone or of estrogens and progesterone together, given similarly to those of Clauberg, Kaufmann and Elden, failed to produce any significant endometrial alterations similar to those occurring during the progestational phase of normal cycles. In a few instances, however, mixed endometria (those with localized or patchy areas of progestational reaction) were encountered after combined therapy with estrogens and progesterone.

The important studies of Venning and Browne<sup>22</sup> in 1936 and 1937 permitted an approach to the clinical investigation of the pharmacology of progesterone which was quite different from those aimed at detecting endometriotropic responses. Venning<sup>23</sup> described a gravimetric method for the quantitation of sodium pregnandiol glucuronide in the urine. She and Browne shortly thereafter submitted evidence that this pregnandiol-complex represented an end-product of the metabolism of progesterone.

All previous studies designed to identify progestin in blood or urine by methods of bio-assay had been singularly unsuccessful. Studies in our clinic<sup>24</sup> have confirmed the fact that the pregnandiol-complex represents an end-product of the metabolism of progesterone. We called attention, however, to limitations necessary in the interpretation of data secured by this method. Our observations were summarized as follows:

(1) Four factors are concerned in the metabolism of progesterone and in the subsequent urinary excretion of sodium pregnandiol glucuronide: (a) *ovarian*, involving the formation of progesterone by post-ovulatory corpora lutea and possibly from the marginal granulosa luteinization of follicles; (b) *endometrial*, concerned with the alteration of progesterone into pregnandiol; (c) *hepatic*, which brings about the conjugation of pregnandiol with glucuronic acid; and (d) *renal*, involving the excretion of sodium pregnandiol glucuronide. (2) The excretion of this compound indicates the functional capacity of all these factors; the absence of the compound from the urine indicates the functional failure of one or more of

TABLE I. DATA REGARDING ENDOMETRIOTROPIC RESPONSES TO CYCLIC THERAPY WITH PROGESTERONE

PATIENT	CYCLES OF THERAPY	ENDOMETRIAL FINDINGS AND ANTECEDENT THERAPY*		
		BEFORE TREATMENT	DURING TREATMENT	AFTER TREATMENT
Case 1	4	E	E 35 (e - p); E 35 (e - p); E-35 (e - p); E- 50 (p)	E-
Case 2	9	E	E- 35 (e - p); M ? 35 (e - p); O 35 (p); M ? 25 (e - p); E 10 (e - p); E 50 (e - e + p); E 50 (e - e + p); E 45 (e - e + p); E 50 (e + p)	O
Case 3	8	M	E 10 (e - p); E 10 (e - p); E 5 (e - p); E 45 (p); M 45 (p); E 25 (p) E 25 (p); O 40 (e - e + p)	E
Case 4	6	E	E 35 (e - p); E+ 35 (e - p); E 35 (e - p); E 40 (p); E 50 (p); E 50 (p).	O
Case 5	1	E+	E 35 (e - e + p)	O
Case 6	7	M	E 40 (p); E 35 (e - e + p); E- 35 (e - p); E 35 (e - e + p); O 35 (e - e + p); E 35 (e - p); E 35 (e - p)	O
Case 7	9	E	O 15 (e - p); E 10 (e - p); E 5 (e - p); E 10 (e - p); E 20 (p); E 10 (p); E 25 (p); E 30 (p); M 15 (p)	O
Case 8	2	M	O 35 (e - p); E 35 (e - e + p)	M
Case 9	7	E+	E 35 (e - p); E 35 (e - p); E 35 (e - p); M 40 (e - p); E 40 (p); E 35 (e - p); E 50 (p)	E
Case 10	2	E	O 40 (p); E 35 (e - p)	O
Case 11	8	E	E 35 (e - p); E 35 (e - p); E 35 (e - p); E 35 (e - p); E 35 (p); E 50 (e + p); M 50 (e + p); E 40 (e + p)	O
Case 12	6	E	E 35 (e - e + p); O 35 (p); E 30 (p); M 50 (p); E 35 (e - e + p); E 45 (e - p)	O
Case 13	8	E+	M 35 (p); M 35 (p); E 35 (p); M 35 (p); E 50 (p); M 50 (p); O 50 (p); M 50 (e + p)	O
Case 14	2	E	O 10 (e - p); E 15 (e - p)	O
Case 15	7	E+	E 35 (p); E 30 (e - p); O 20 (e - p); M 35 (e - p); O 35 (e - e + p); E 35 (e - e + p); O 35 (e - e + p)	E
Case 16	6	E+	M 35 (p); E 45 (p); E 45 (p); O 45 (p); E 30 (p); O 50 (p)	E
Case 17	5	E	E+ 30 (p); E+ 35 (e - e + p); O 35 (p); E 25 (e - e + p); E 45 (e + p)	O
Case 18	3	E	E 35 (e - e + p); E 35 (e - e + p); E 35 (e - e + p)	O
Case 19	3	M	M 65 (e + p); E 45 (e - e + p); P 40 (e + p)	O
Case 20	2	E	M 50 (e - p); E 35 (e - p)	O
Case 21	4	E+	O 30 (e - p); M 25 (e - p); M 40 (e - e + p); E 30 (e - p)	O
Case 22	4	E	O 15 (p); E 60 (p); O 40 (p); M 40 (e + p)	O
Case 23	5	E	E 10 (e - p); E 20 (e - p); M 20 (e - p); M 40 (e - p)	M

\*The endometrial findings are designated by the symbols, E, E-, E+, M and P as explained in the text. When O appears instead of these symbols, no endometrial specimen was obtained. The numerals following the endometrial symbols, indicate the amount of progesterone in mg. given prior to the time the specimen of endometrium was obtained. There follow next symbols denoting the character of treatment; (e - p) estrogens followed by progesterone; (e - e + p) estrogens followed by estrogens and progesterone given concurrently; (e + p) estrogens and progesterone given concurrently; and (p) progesterone given alone.

amount calculated to be present rather than the amount actually extracted (i.e., added a correction for the percentage of a known amount not extractible by the method employed).

#### ENDOMETRIOTROPIC DATA

These data were obtained during the course of 117 series of cyclic therapy with ovarian sterols given 23 women with functional irregularities of uterine bleeding. All preparations of these sterols were employed in solutions of oil and were given intramuscularly. The ages of these women varied from 12 to 37 years, the majority being under 25 years of age.

The endometrial findings are designated by the following symbols, according to a system of classification<sup>25, 26</sup> employed in our clinic:

- E- hypoestrogenic or atrophic endometrium.
- E persistent estrogenic endometrium.
- E+ hyperestrogenic or hyperplastic endometrium.
- M mixed or irregularly ripened endometrium.
- P progestational endometrium.

These clinical data are presented in Table I.

Each patient received an average of approximately 5 cycles of therapy. The greatest number of cycles was 9; each of 2 patients received this number. The smallest number of cycles of therapy was 1; this was given only 1 patient.

The 117 cycles of therapy were distributed as to kind as follows:

Estrogens* followed by progesterone (e - p)	46 cycles
Estrogens followed by estrogens and progesterone (e - e + p)	21 cycles
Estrogens and progesterone (e + p)	9 cycles
Progesterone alone (p)	41 cycles
Total	117 cycles

The total doses of progesterone given during the 117 cycles varied from 5 to 65 mg. The frequency of the different doses was as follows:

5 mg.	2 cycles	20 mg.	4 cycles
10 mg.	8 cycles	25 mg.	6 cycles
15 mg.	4 cycles	30 mg.	7 cycles
		35 mg.	47 cycles
40 mg.	12 cycles	60 mg.	1 cycle
45 mg.	9 cycles	65 mg.	1 cycle
50 mg.	16 cycles		

The total amount of progesterone given was 4,045 mg. The average dose for a cycle of therapy was 34.5 mg.

A total of 129 endometrial specimens was studied: 23 before treatment; 99 during therapy; and 7 after the discontinuation of therapy.

Before therapy the endometrial findings were distributed as follows:

E (persistent estrogenic)	13 patients
E+ (hyperestrogenic)	6 patients
M (mixed)	4 patients
Total	23 patients

\*The estrogens employed in these studies were estrone and estradiol benzoate.

Case 26 is presented only by protocol: (The record of this patient has been reported previously by our group.<sup>24</sup>) She was a white girl, aged 17 years, who was referred for the treatment of delayed adolescence and menarche. Examination showed a developmental status comparable to the late juvenile epoch. The uterus and cervix corresponded in size and contour to this stage of development.

Preliminary therapy with an anterior pituitary extract, containing gonadotropic and thyrotropic fractions, yielded no significant clinical responses. Cyclic treat-

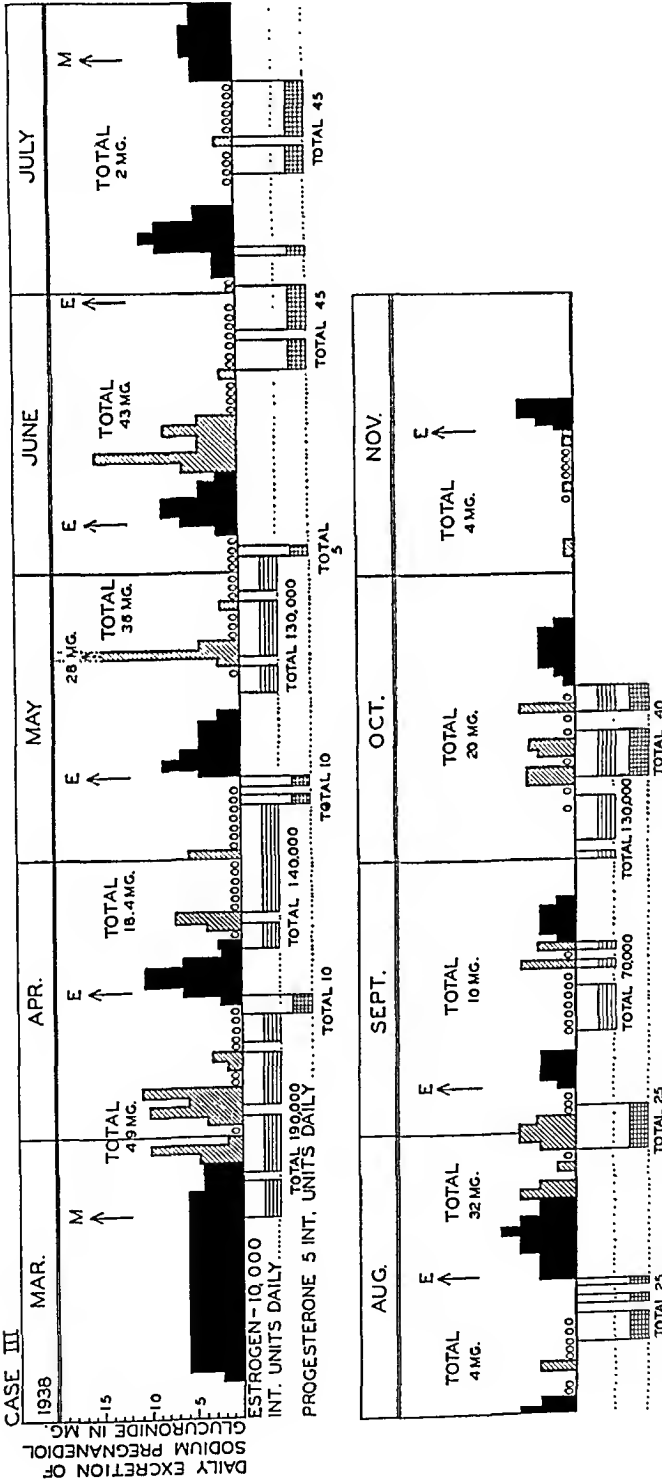


Fig. 1A.—Case 3.\* A colored woman, aged 22 years, married, para 0-0-0, had had no metrorrhagia except that charted. Her period preceding the episode of bleeding in March had occurred February 18 and lasted until February 22. Endocrine and gynecologic surveys showed nothing significant. Treated cyclically with steroids as charted. Treatment was discontinued in October.

Explanation of symbols and abbreviations used in Figs. 1, 2, and 3. Curettage is indicated by ↓, biopsy by ↑. Menstrual flow is indicated quantitatively in terms of saturated pads by the solid black blocks. The urinary excretion of sodium pregnanol glucuronide is shown by the shaded blocks. When determinations were made and negative values obtained, these are indicated by 0. Endometrial findings are indicated by E-, E, E+, M and P, the significance of which has been explained in the text.

\*The March to June cycles in Case 3 and January to June cycles in Case 7 have been reported previously by one of us (E.C.H.: Endocrinology 24: 13, 1939).

During treatment the following frequency of the endometrial findings occurred:

E (persistent estrogenic)	70 occurrences
E+ (hyperestrogenic)	3 occurrences
E- (hypoestrogenic)	4 occurrences
M (mixed)	21 occurrences
P (progestational)	1 occurrence
Total	99 occurrences

After the discontinuation of treatment, in 15 of the 23 patients, the following findings occurred:

E (persistent estrogenic)	4 patients
E- (hypoestrogenic)	1 patient
M (mixed)	2 patients
Total	7 patients (8 failed to return for examination)

The endometrial findings during therapy of the 4 patients who had mixed (M) endometria prior to treatment may be summarized as follows: a total of 3 specimens of the entire 17 examined showed progestational reaction (2M and 1P).

The therapy which preceded each specimen, in which some degree of progestational response was observed, may be analyzed as follows:

Treatment with estrogens followed by progesterone	8 instances
Treatment with estrogens followed by estrogens and progesterone	1 instance
Treatment with estrogens and progesterone	5 instances
Treatment with progesterone, alone	8 instances
Total occurrences of M and P	22 instances

The total doses of progesterone which preceded the finding of a M or P endometrium were as follows:

15 gm.	1 instance	40 mg.	6 instances
20 mg.	1 instance	50 mg.	5 instances
25 mg.	2 instances	65 mg.	1 instance
35 mg.	6 instances		
Total			22 instances

The average dose of progesterone which was associated with a progestational response (M and P) was 38.6 mg. (Somewhat higher than the average dose given, 34.5 mg.)

#### DATA FROM DETERMINATIONS OF URINARY TITERS OF SODIUM PREGNANDIOL GLUCURONIDE

These data are based upon 40 cycles of 7 patients who had received cyclic therapy similar to those reported in Table I. Since 4 of these patients (Cases 3, 7, 22, and 23) were studied for endometriotropic responses, their records have been included also in Table I. The significant data secured from 6 of these 7 patients (Cases 3, 7, 22, 23, 24, and 25) are presented graphically together with brief protocols in Figs. 1 to 3.\*

\*The dosage of progesterone in these charts is given in terms of international units. One international unit of progesterone is equivalent to 1 mg.

All daily urinary specimens were consistently negative for sodium pregnandiol glucuronide during the entire period of therapy.

The data secured from the determinations of the urinary titers of sodium pregnandiol glucuronide of 7 patients are presented in Table II.

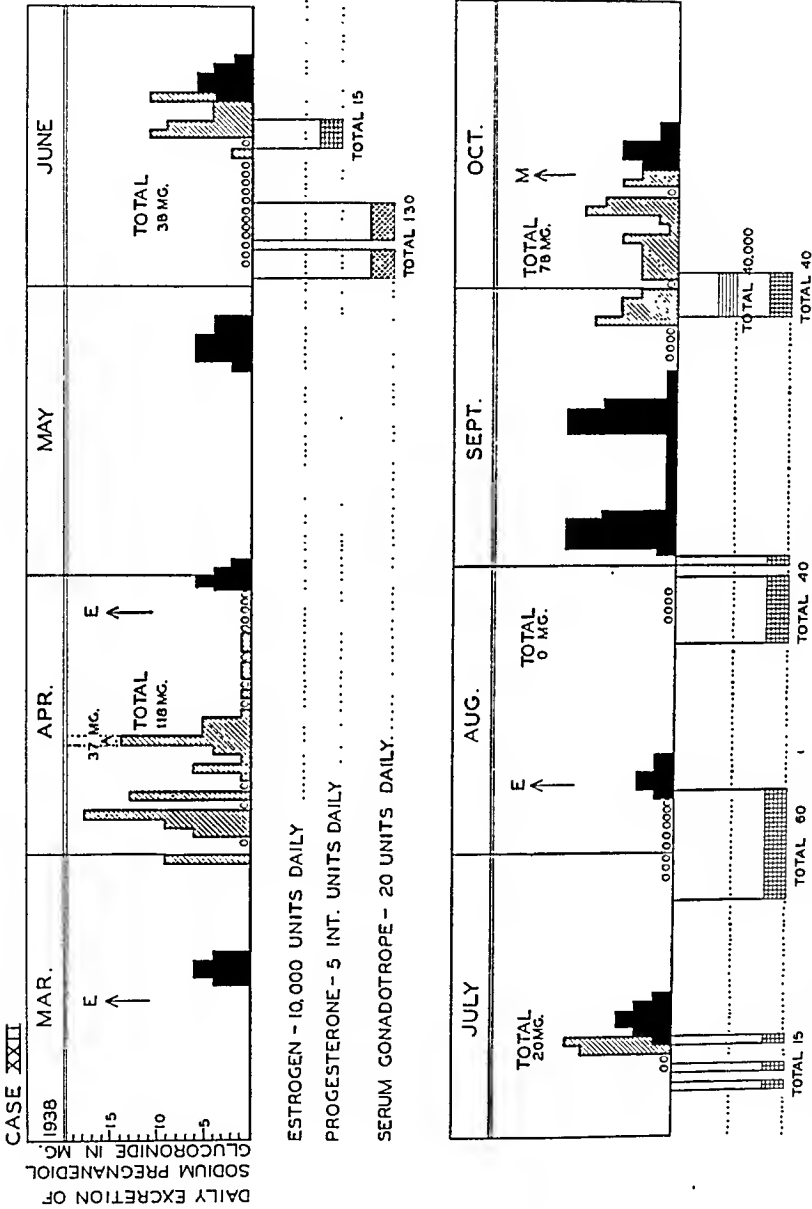


Fig. 24.—Case 22. A white woman, aged 30 years, married, para 0-0-0, had had absolutely irregular bleeding since menarche at 13 years of age. Intervals between episodes of flowing varied from five weeks to three months. Flow usually lasted three to five days and was not excessive. Patient sought treatment because of presumed sterility during her six years of marriage. Endocrine and gynecologic surveys yielded no significant findings. The cycle in June, when gonadotropes were given, is not considered in the data reported. Treatment has been discontinued.

The details of therapy have been discussed and are demonstrated graphically in Figs. 1 to 3. Combinations of estrogens (estrone and estradiol benzoate) with progesterone were employed for their presumed synergistic effects upon the utilization and metabolism of progesterone. Estriol or estriol glucuronide were not employed, although the recent studies of the Smiths<sup>27</sup> indicate a possible close association of this estrogen with the metabolism and utilization of progesterone. In collecting the data summarized in Table II from those presented in Figs. 1 to 3, an arbitrary system of selection was carried out as follows: No therapy was counted if urines were not available for at least twenty-four hours after it was given; all

ment with the ovarian sterols was given. During this treatment daily twenty-four-hour specimens of urine were studied for titers of sodium pregnandiol glucuronide.

Treatment was given as follows: from April 13 to 28 inclusive, 10,000 I. U. of estrogen (estrone) were given intramuscularly daily, resulting in a total dosage of 140,000 I.U. From April 29 to May 6, inclusive, 5 mg. of progesterone were given intramuscularly daily, making a total dosage of 35 I.U. From May 13 to 20, inclusive, 20,000 I.U. of estrone were given intramuscularly daily and from May 21 to May 28, inclusive, 10,000 I.U. were administered similarly, making a total dosage of 200,000 I.U. of estrone. No bleeding followed these treatments despite the fact that some enlargement of the breasts and uterus occurred.

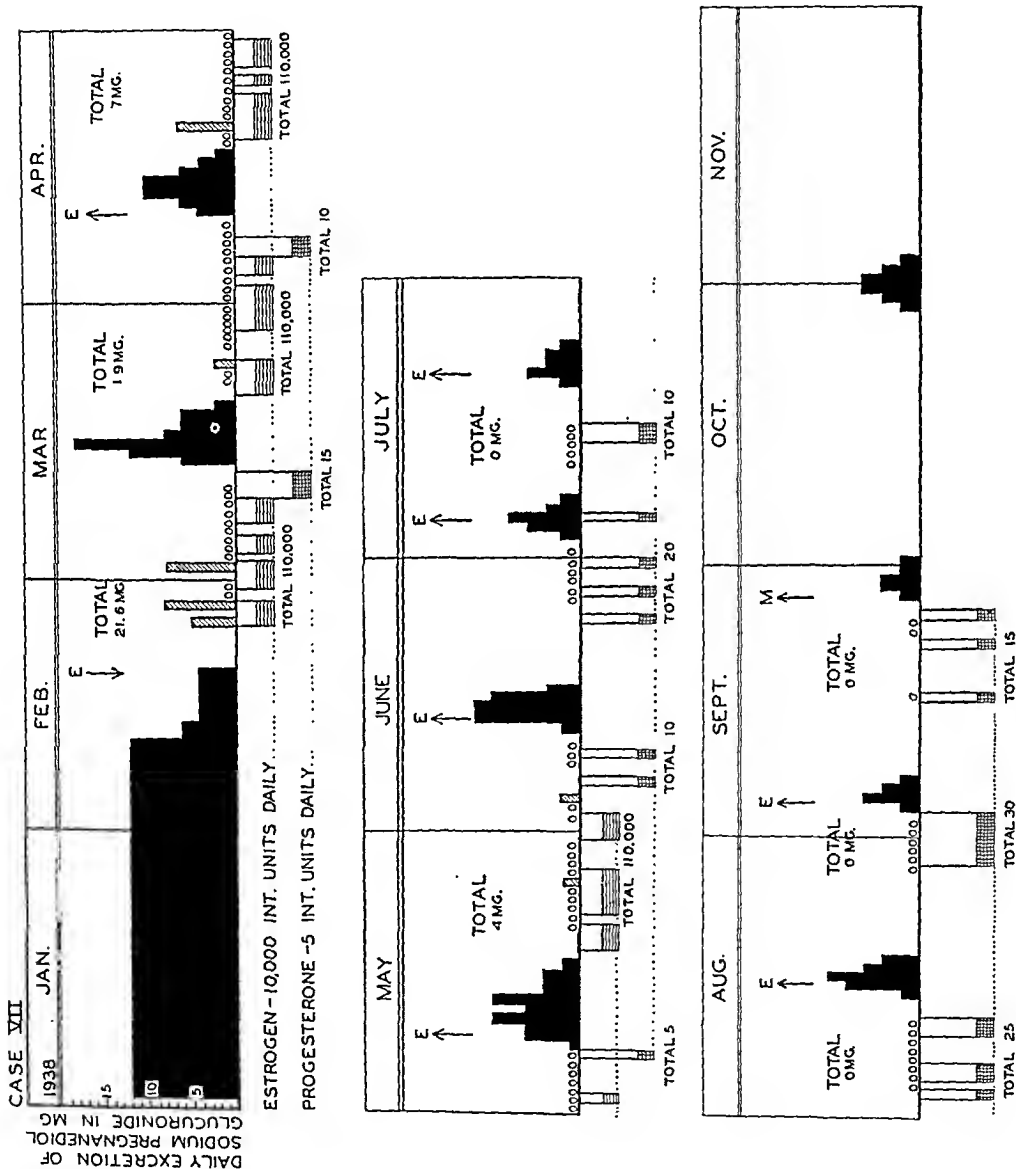


Fig. 1B.— Case 7.\* A colored woman, aged 20 years, single, had had excessive and depleting metrorrhagia for one year. She was admitted to hospital February 9, at which time her hemoglobin was 11 per cent and erythrocytes 1,150,000. After multiple transfusions, a curettement was done February 16. Endocrine and gynecologic surveys were not significant. Treated cyclically with sterols as charted. Treatment was discontinued in September.

\*See footnote to Fig. 1A.



Selective segregation of these data indicates that during the time when 340 mg. of the 435 mg. of progesterone administered alone was given, no pregnandiol-complex was recovered in the urine.

The endometrial findings in Cases 3, 7, 22, and 23 have been summarized in Table I.

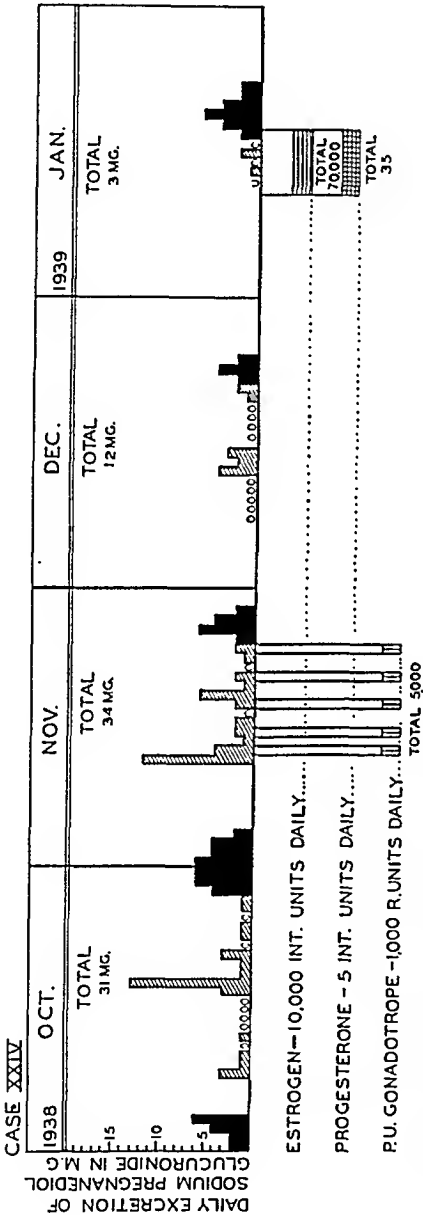


Fig. 3A.—Case 24. A white woman, aged 31 years, married, para 1-0-1, had had hypomenorrhea for some six years and for eighteen months had gained weight, had had a moderate hypertension and had experienced an itchy erythema of face, upper arms, and chest. Endocrine survey led to a tentative diagnosis of early pituitary basophilism. Gynecologic examination yielded no significant data. The month of November, when treatment with P.U. gonadotropes was carried out, is not included in the data reported. Treatment with sterols continues.

DISCUSSION

In a previous communication<sup>25</sup> we have referred to the effectiveness of cyclic therapy with the ovarian sterols in functional menometrorrhagia. The additional patients reported in this study give further proof of this desirable clinical response. It was suggested in the previous report that the effect of this form of therapy was exerted probably to a large degree upon the functional capacity of the pituitary.

sodium pregnandiol glucuronide excreted for seventy-two hours after the last injection of progesterone was credited to therapy.

All of the patients, except the one described in Case 26, excreted sodium pregnandiol glucuronide derived from their endogenous sterols. The larger number of determinations, done during times when no progesterone was given, was designed to estimate and evaluate this source of the pregnandiol-complex.

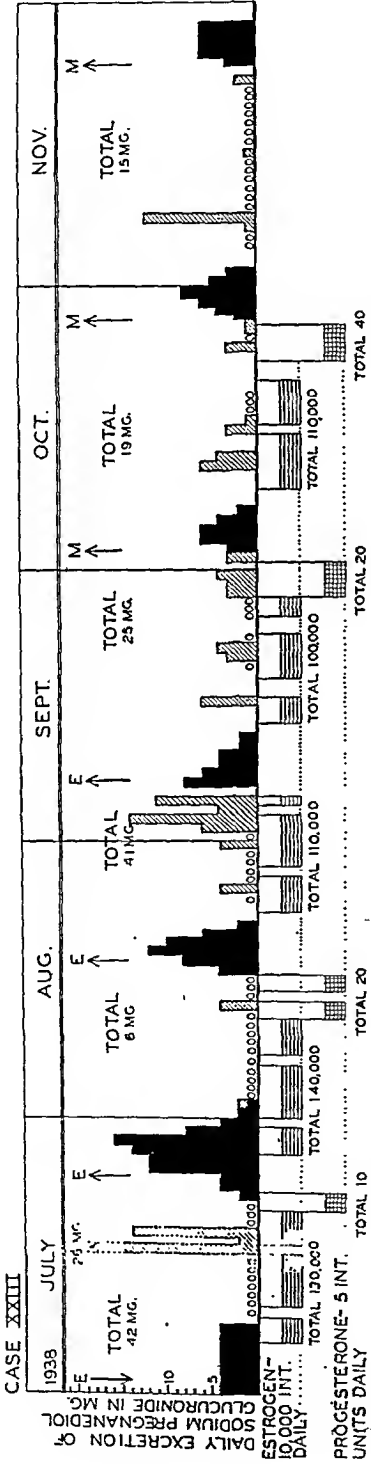


Fig. 2B.—Case 23. A colored woman, aged 17 years, single, had had polymenorrhea and hypermenorrhea for two years. A prolonged and depleting episode of metrorrhagia which began in January, 1938, lasted until curettage in July (see chart). At the time of admission to hospital July 1, 1938, the hemoglobin was 18 per cent and the erythrocytes were 1,950,000. Endocrine and gynecologic surveys yielded no significant data. Treatment with sterols was discontinued in October.

TABLE II. DATA SECURED FROM STUDIES OF URINARY TITERS OF SODIUM PREGNANDIOL GLUCURONIDE OF 7 PATIENTS WHO RECEIVED CYCLIC THERAPY WITH OVARIAN STEROLS

THERAPY	AMOUNT OF PROGESTERONE GIVEN	AMOUNT OF ESTROGENS GIVEN	SODIUM PREGNANDIOL GLUCURONIDE				
			NUMBER OF DE- TERMINATIONS MADE	AMOUNT ACTUALLY RECOVERED	AMOUNT TO BE EXPECTED* IF METABOLISM AND RE- COVERY WERE COMPLETE	PER CENT OF THEORETICAL YIELD ACTUALLY RECOVERED	AVERAGE RECOVERY PER DETERMINATION
Progesterone alone	Mg. 435	I.U.	95	Mg. 61.0	Mg. 739.5	% 8.2	Mg. 0.64
Progesterone and es- trogens given con- currently	140	270,000	29	37.0	238.0	15.5	1.27
Estrogens alone	0	1,990,000	216	285.4			1.32
No medication	0	0	186	340.0			1.84
Progesterone given but not correlated with the output of preg- nandiol-complex	60						
Total	635	2,260,000	526	723.4			

\*This is calculated upon the assumption that each molecule of progesterone (molecular weight 314) is converted into a molecule of sodium pregnandiol glucuronide (molecular weight 536), thus, amount of progesterone in mg.  $\times$  536/314 or 1.7 = amount of sodium pregnandiol glucuronide in mg.

A spread of treatments over a longer range of the cycle may prove more effective.

The endometriotropic effectiveness of this dosage when given in the manner described was only approximately 1 per cent, if the development of a generalized progestational response is accepted as a measure of it: only 1 normal progestational endometrium was encountered during the 99 cycles of therapy, the results of which were sampled by endometrial biopsies at the appropriate time.

If one accepts the occurrence of any evidence of progestational response (the presence of mixed endometria, having localized, patchy areas of progestational alteration), then the effectiveness of this therapy is approximately 22 per cent, for 22 mixed and progestational endometria were encountered after the 99 cycles of therapy.

This apparent ineffectiveness of progesterone does not seem definitely related to the lack of endometrial "priming" by estrogens. The concurrent administration of estrogens and progesterone is apparently the most effective form of therapy. It was employed only 9 times, resulting in some progestational alteration in 5 instances. The concurrent administration of estriol or estriol glucuronide and progesterone was not done. It should be tried.

The apparent inability of progesterone to be utilized effectively by the endometria of these patients for progestational alterations may be

The endometriotropic responses to it have not been striking. A study of these for evidence of effective utilization of injected progesterone is our present concern.

The dosage of progesterone employed has been essentially that adopted generally as the amount deemed necessary for producing a full progestational response of the endometrium. Some authors<sup>28</sup> have

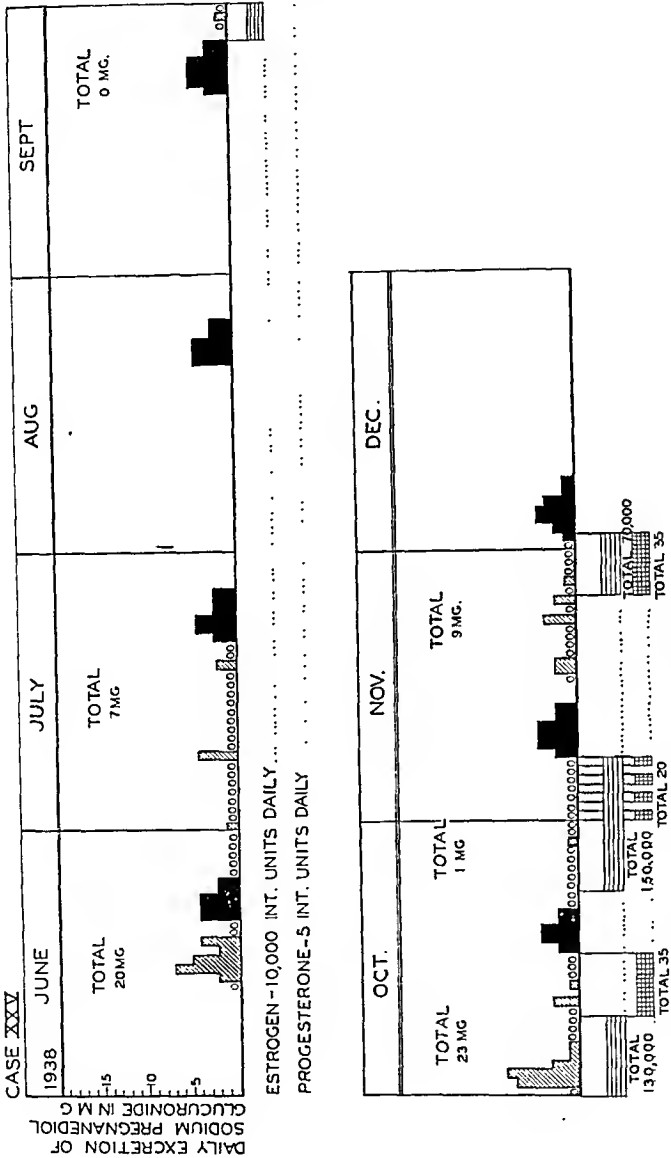


Fig. 3B.—Case 25. A white woman, aged 34 years, married, para 0-0-0, had had epileptiform convulsions in association with menstruation for two years. Endocrine, neurologic and gynecologic surveys yielded no significant data except for a low urinary titer of sodium pregnandiol glucuronide. There was a history of oligomenorrhea with episodes of amenorrhea during the eighteen months, prior to the time covered in the chart. The menses charted, however, were quite regular. Treatment with sterols was discontinued the first of December.

accepted the doses employed by Kaufmann<sup>19</sup> and Clauberg<sup>18</sup> as representing the possible cyclic output of the corpus luteum. The average dose for a series given by us has been 34.5 mg., one in good agreement with the theoretical amount necessary. During only 24 of the 117 cycles reported was the total dose less than 30 mg. An analysis of the doses which preceded the occurrence of some degree of progestational alteration does not indicate that the amount given was too small.

however, it is recalled that the average recovery for each determination was 1.32 mg. when only estrogens were given and 1.84 mg. when no therapy was given, it seems warranted to conclude that apparently no definite metabolism of the progesterone injected alone occurred. During its administration, as a matter of fact, there is a possibility that a depression of the metabolism of intrinsic progestin resulted.

The endometriotropic data and, perhaps, those concerned with the urinary titers of the pregnandiol-complex possibly indicate that the occurrence of a more effective metabolism and utilization of progesterone when it and the estrogens are given simultaneously. Recent studies on rabbits emphasize close correlations in the functions of these two groups of sterols: Courrier and Kehl<sup>32</sup> have reported that the involution of a progestational endometrium, which occurs despite continued injections of progesterone, is retarded by the simultaneous administration of estradiol and progesterone; Heckel and Allen<sup>33</sup> have found that injections of estrogens during the latter part of pregnancy result in an inhibition of parturition, apparently due to a maintenance of the functional capacity of the corpus luteum.

Since, however, the average recoveries of the pregnandiol-complex per determination during the administration of estrogens and during that of estrogens and progesterone conjointly were practically identical, one may assume that any alterations were due to effects exerted by the estrogens on the metabolism of the intrinsic progestin of these patients. The high value of the average recovery of the pregnandiol-complex during the intervals when no treatment was given is probably not significant, since it is due to the inclusion of data secured from the long first cycle of Case 22 when an unusually large amount (118 mg.) of the pregnandiol-complex was excreted.

Venning and Browne<sup>34</sup> have reported that in some instances the conjoint administration of progesterone and pregnancy-urine gonadotropes resulted in a greater excretion of the pregnandiol-complex than when progesterone alone was given. Our group<sup>35</sup> has made similar observations, and we have encountered in some instances striking enhancement of these values when estrogens, pregnancy-urine gonadotropes and progesterone are given simultaneously.

Many of the difficulties which are apparent in attempts to evaluate the data presented in this study would not be encountered in a group of women having no metabolism of their intrinsic progestin. For this reason, similar studies should be made upon oophorectomized women.

#### SUMMARY

Studies have been reported upon the endometriotropic responses of 23 patients with functional irregularities of uterine bleeding during 99 of 117 cyclic series of therapy with progesterone alone or combined with estrogens. During 30 cycles of 4 of these patients, and during 10 cycles of an additional group of 3 patients, similarly treated, urinary titers of sodium pregnandiol glucuronide were determined.

related either to a refractivity of these endometria, or to the lack of some factor necessary to render utilization possible, or to the fact that progesterone cannot be metabolized and utilized when given in the form and manner generally employed clinically. The data secured from studies of the urinary titers of sodium pregnandiol glucuronide have some bearing upon these possibilities just mentioned.

In the instances of 6 of the 7 patients, whose urinary titers of sodium pregnandiol glucuronide were investigated, there is no reason to assume that any factors existed which disturbed the normal metabolism of progestin, for all of these 6 patients excreted varying amounts of the pregnandiol-complex before any treatment was given. The source of this must be related to the existence of an effective mechanism for the metabolism of the intrinsic progestin supplied by their own ovaries. These patients, however, as a study of their endometriotropic responses indicates, were not utilizing their own progestin effectively. There was either some necessary factor for this which was absent or a refractivity of the endometria existed. It may be assumed that similar conditions may have existed in some of the other patients not investigated in this regard.

Since these patients were able apparently to metabolize their own intrinsic progestin, it would be expected that they would be able to metabolize also that injected intramuscularly as progesterone. We have reported,<sup>24, 29</sup> however, that there exists some evidence that this extrinsic progesterone is not metabolized. Stover and Pratt,<sup>30</sup> furthermore, have reported the injection of 15 and 17.5 rabbit units of progestin as contained in an extract of corpora lutea (lipo-lutin) without being able to recover any of the pregnandiol-complex from the urines of the patient, although they carried out determinations for 12 consecutive days after the last injection. They call attention, however, to the fact that Venning and Browne<sup>31</sup> had reported that they had injected 19, 28, and 30 mg. of progesterone in 3 different women with recoveries of the pregnandiol-complex comparable to a yield of 46, 40, and 12 per cent, respectively.

Our data do not indicate that the progesterone given intramuscularly to the 7 patients reported was metabolized in such a manner as to result in any significant increases in the urinary titers of sodium pregnandiol glucuronide. Despite an intrinsic output of the pregnandiol-complex, the amount recovered during the administration of progesterone alone was equivalent to only 8.2 per cent of the theoretical yield to be expected from the metabolism of the extrinsic progesterone. When estrogens were given concurrently with progesterone, the total yield of the pregnandiol-complex was only 15.5 per cent of that to be expected from progesterone given had it all been metabolized into sodium pregnandiol glucuronide.

Similar differences apparently exist when the average recovery for each determination is examined: during the administration of progesterone this figure was 0.64 mg., while during the administration concurrently of estrogens and progesterone, it was 1.27 mg. When,

## TOXEMIA MORTALITY IN THE SOUTHERN STATES\*

A CRITICAL STUDY OF 577 MATERNAL DEATHS IN NORTH CAROLINA  
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THE percentage of maternal deaths in the South from the toxemias of late pregnancy is strikingly high when compared to other sections of the United States, and presents a peculiar sectional problem worthy of consideration. The map (Fig. 1) of the United States, prepared by the Children's Bureau of the United States Department of Labor, presents in a clear-cut manner the "toxemia belt" as related to maternal mortality. In a group of eight adjoining southern states nearly one-third of all maternal deaths are due to the toxemias of late pregnancy (Fig. 1).

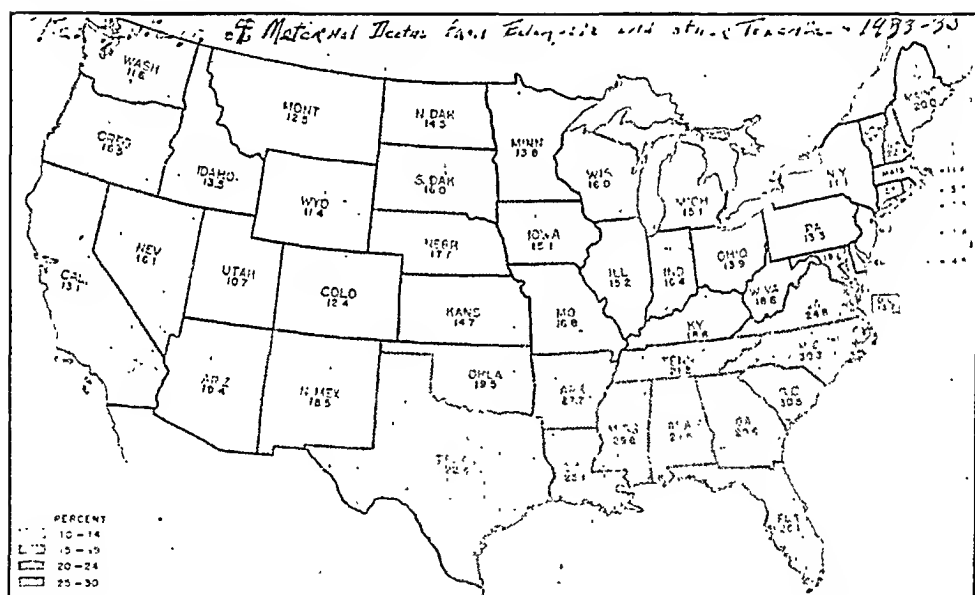


Fig. 1.—Percentage of maternal deaths from eclampsia and other toxemias, 1933 to 1935. (U. S. Dept. of Labor, Children's Bureau.)

It was believed that a study of atmospheric conditions in various states of the Union and their comparison with these southern states, together with a detailed analysis of a large number of maternal deaths from late pregnancy toxemia in one southern state, might disclose factors contributing to this appalling loss of maternal life and its sectional distribution.

With the aid of the United States Weather Bureau, the average rainfall of each state in the Union was ascertained, together with

\*Presented at a meeting of the South Atlantic Association of Obstetricians and Gynecologists, Charleston, S. C., February 11, 1939.

The endometriotropic data warrant the conclusion that crystalline progesterone, when administered intramuscularly in oil to women with functional irregularities of uterine bleeding, is inefficiently utilized. Six of the 7 patients studied were also unable to utilize efficiently their intrinsic progestin despite the existence of evidence that it was being metabolized normally.

The intramuscular administration of crystalline progesterone to these patients resulted not only in no increases in their urinary titers of the pregnandiol-complex but also in apparent decreases. These observations suggest that incomplete metabolism occurred.

Some of the various factors which may influence the metabolism and utilization of progesterone are discussed.

The authors are indebted to the following commercial organizations for generous supplies of the sterols used in these studies: Schering Corporation for progynon-B (estradiol benzoate) and proluton (progesterone); Parke, Davis & Co. for theelin (estrone); E. R. Squibb and Sons for amniotin (estrone). They are grateful to their assistants, Catherine Ashley and Margaret Baptist, for their help with determinations of the urinary titers of sodium pregnandiol glucuronide. A part of the expenses incurred in these studies was defrayed by funds allotted through a grant of the Research Council of Duke University to one of us (E.C.H.).

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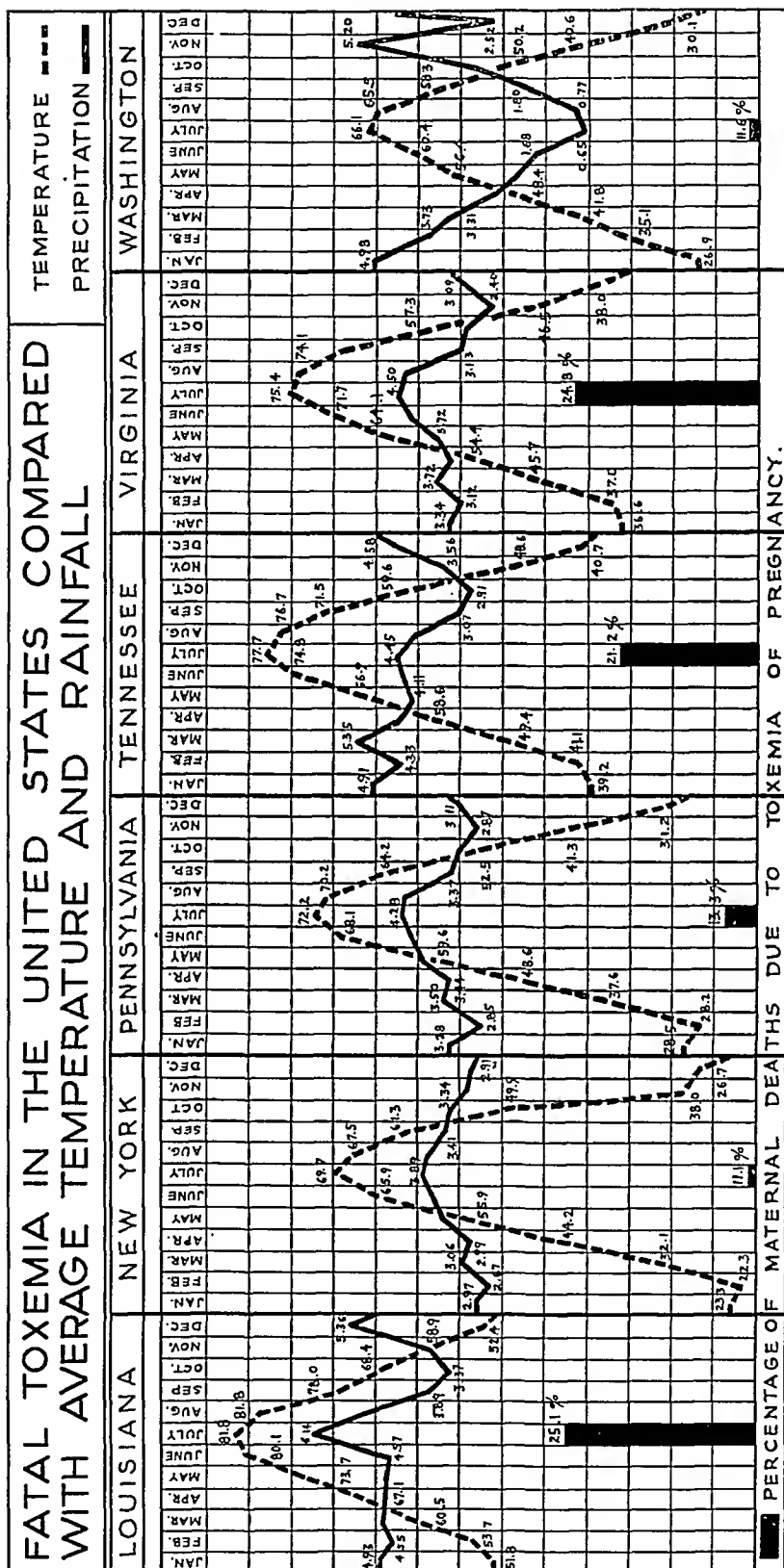


Fig. 2.

average monthly temperature, humidity, percentage of sunshine, etc. It became immediately apparent that the percentage of maternal deaths from toxemia of pregnancy was highest in those states with the highest annual rainfall, but only where the season of rainfall was accompanied by a relatively high temperature. It was found to be generally true that the southern states had a high temperature during the months of greatest precipitation, and it is in these states that toxemia exacts its terrific toll (Florida, Louisiana, Virginia, Tennessee, North Carolina, etc.).

Upon investigating average monthly temperatures in other sections of the country, it was found that a reduction of rainfall during the hot months or heavy precipitation during the colder months was the trend in states with a low maternal mortality from toxemia. For example, both Washington and California, while states with a high precipitation, have a low temperature during the months of greatest rainfall and only a small percentage of the maternal deaths in these states is due to toxemia (Figs. 2 and 3). Also states that are naturally dry throughout the entire year, such as Colorado, have a small percentage of their maternal deaths from toxemia. As the rainfall increases with rising temperature, the tendency is toward an increase in fatal toxemia (Illinois, Indiana).

Another exception to the general trend of a high percentage of maternal deaths from toxemia in states with heavy rainfall associated with high temperature was found in those states with highly organized and well-advanced maternal welfare programs. In this classification are states with concentrations of population, as New York with 11.1 per cent of maternal deaths from toxemia, New Jersey 11.8 per cent, and Pennsylvania 13.3 per cent. It was impossible to establish any relationship between humidity, sunshine, and eclampsia. These findings are somewhat confirmatory of Dieckmann's<sup>1</sup> conclusions that eclampsia flourishes in a hot, wet climate.

In 1932 the Bureau of Vital Statistics of the North Carolina State Board of Health initiated a five-year study of maternal deaths in North Carolina. A detailed questionnaire was sent to every physician who signed a death certificate on which some condition relating to pregnancy was given as the cause of death. Of the 2,746 questionnaires, 58 per cent were returned with acceptable information. A total of 577 questionnaires reporting eclampsia, hypertension, albuminuria, or other toxemias of pregnancy as the cause of death were personally studied in detail and form the basis of the statistical data herein reported (Fig. 4).

There were 344 fatal cases of eclampsia and 171 nonconvulsive fatalities from late pregnancy toxemia with albuminuria and/or hypertension, which, together, accounted for 32.3 per cent of all the maternal deaths reported. There were 62 additional fatalities classified as due to "other toxemias of pregnancy," which, according to this survey, constitute 3.9 per cent of the maternal deaths in North Carolina.

The high percentage of maternal deaths from puerperal albuminuria and particularly eclampsia in North Carolina, as found by this detailed investigation, is in accord with the findings of other investigators who have repeatedly reported the high incidence of convulsive toxemia in the southern states.<sup>2-4</sup>

### 344 MATERNAL DEATHS FROM ECLAMPSIA IN NORTH CAROLINA

The 344 maternal deaths from eclampsia were separated into the months in which death occurred, and a chart prepared showing this in relation to the average monthly temperature and rainfall in North Carolina. It is evident that there were more fatal eclamptic cases during the months of greatest precipitation and temperature, but quite apparent that the distribution of death permits of many other factors and causes (Fig. 5).

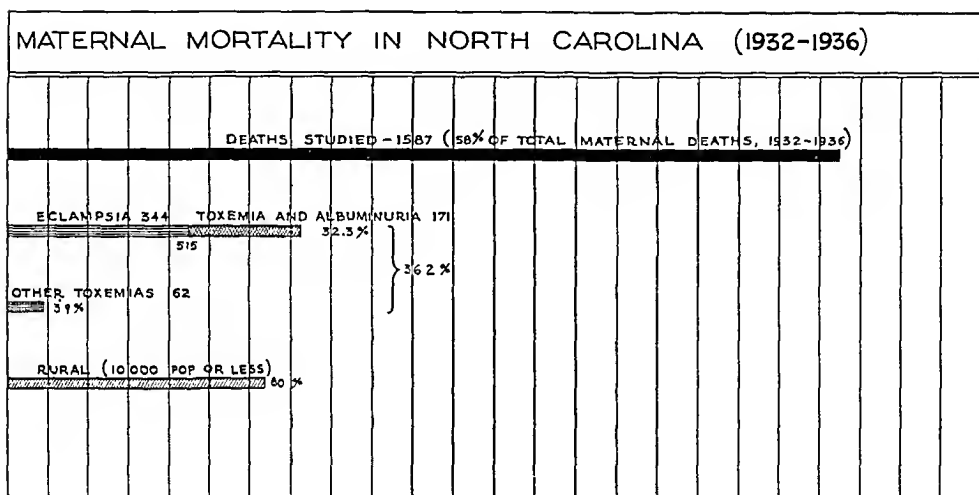


Fig. 4.

Fifty-one per cent of the 344 eclamptic patients died in North Carolina hospitals. During the past ten years there has been an increase in the percentage of hospital births in North Carolina from 5 per cent to approximately 20 per cent. According to the hospital section of the Duke Endowment, in 1926 there were 150 patients with eclampsia hospitalized in North Carolina, constituting 4.7 per cent of the hospital deliveries, with 35 maternal deaths, an eclamptic mortality rate of 23.33 per cent. In 1937 there were 332 cases of eclampsia, constituting 2.8 per cent of a total of 11,704 hospital births with 41 fatalities, an eclampsia mortality rate of 12.35 per cent (Fig. 6).

In 1926, 51 per cent of all maternal deaths occurring in North Carolina hospitals were due to eclampsia. With the increase in the number of hospital births and probably aided by a more conservative treatment of the active eclamptic patient, there has been a gradual reduction of this figure. In 1937, in the 81 nonprofit hospitals operated under the Duke Endowment, 29 per cent of all the maternal deaths were reported as due to eclampsia.

Eighty per cent of the fatal cases of eclampsia in North Carolina occurred in rural areas or in towns of less than 10,000 population. As 85 per cent of the population of North Carolina is found in communities of 10,000 or less, this figure is commensurate with the distribution of population. Hospitalization of the 163 institutional deaths was a last resort in many patients who arrived in extremis. One institution with a large obstetric service reported a total of 3 fatal cases of eclampsia in five years, the deaths occurring one, two, and five hours, respectively, after hospital admission.

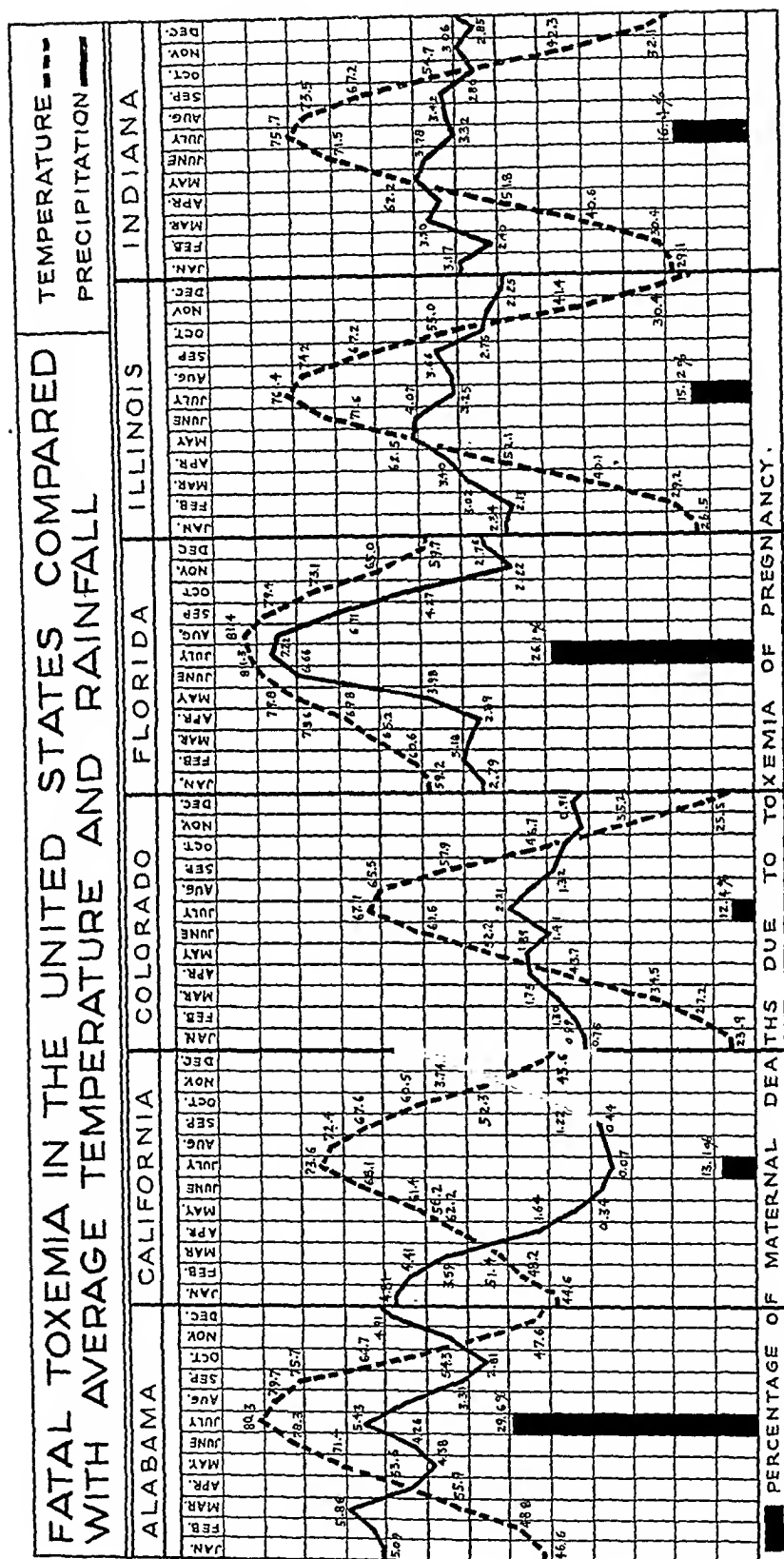


Fig. 3.

pared to 7.6 per cent illegitimacy of all births occurring in North Carolina in 1936. Forty-two and one-tenth per cent of the patients (144 cases) of the fatal cases of eclampsia were colored, as compared to a negro incidence of approximately 30 per cent of the annual births in North Carolina. Forty-four per cent of the 344 fatalities from eclampsia occurred in multiparas. Two out of 5 of these patients gave a definite history of toxemia in a previous pregnancy. Doubtless this figure would be higher with more complete and accurate histories.

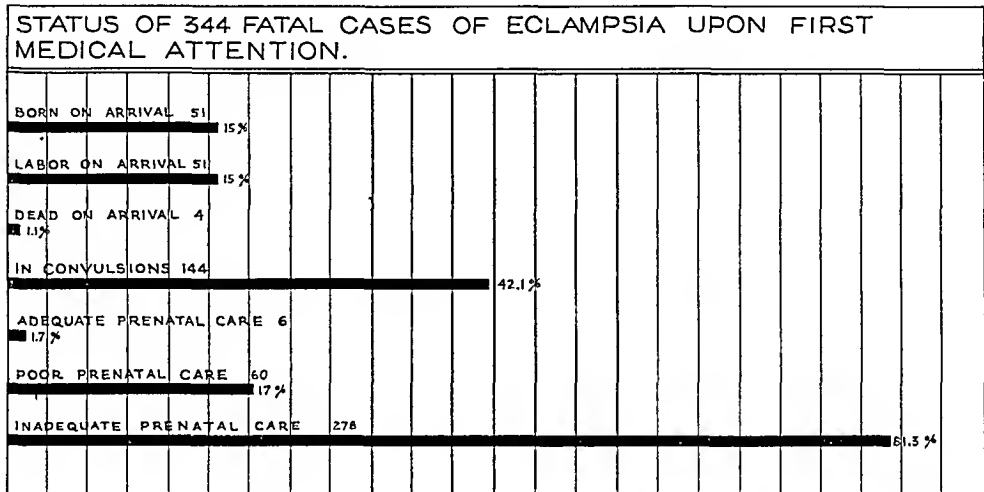


Fig. 7.

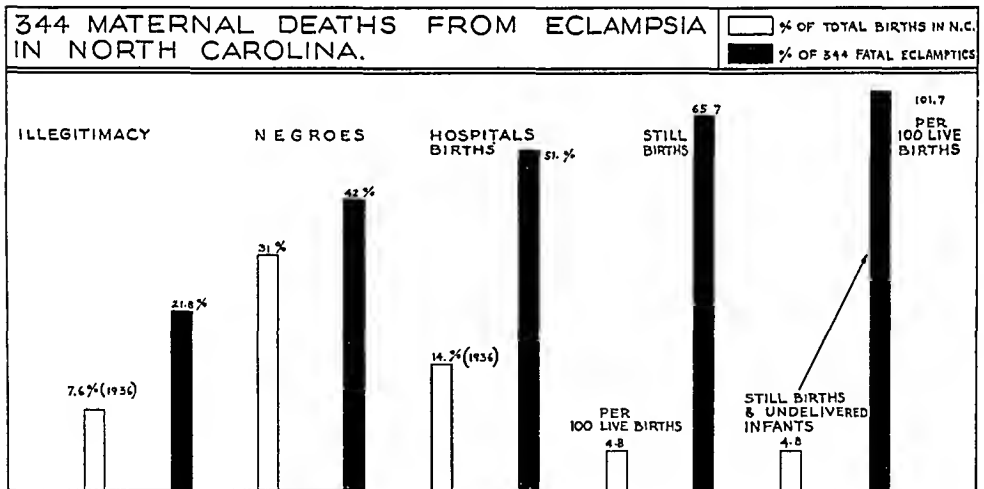


Fig. 8.

There were 245 infants delivered by physicians with a 50 per cent operative interference (Fig. 9). In 117 of the 122 operative deliveries, the only indication given for obstetric surgery was the pregnancy toxemia. The other indications consisted of hemorrhage in 4 cases and disproportion in 1. On these 122 cases, 175 operations were performed, consisting of 41 versions, 43 dilatations of the cervix, 38 low forceps, 13 midforceps, 9 high forceps, 10 cesarean sections, 3 breech extractions, 5 bag or bougie inductions, 6 cases of manual removal of the placenta, 6 extensive repairs, and 1 craniotomy. One patient died as a result of spinal anesthesia. Two deaths illustrate the danger of pituitary extracts in acute vascular spasm, as death immediately followed administration of pituitrin in one and thyrophysin in another.

Only 6 patients of the 344 fatal cases of eclampsia had adequate and good prenatal care, apparently dying of an overwhelming fulminating convulsive toxemia. Sixty (17 per cent) had negligent or inadequate prenatal care. While it is impossible to establish accurately the responsibility for this group of 60 maternal deaths of patients who were under medical supervision, the basic factors were apparently well distributed between negligence on the part of the patient and indifferent supervision on the part of the physician in the presence of warning symptoms and alarming physical findings.

### FATAL ECLAMPSIA IN NORTH CAROLINA COMPARED WITH AVERAGE TEMPERATURE AND RAINFALL.

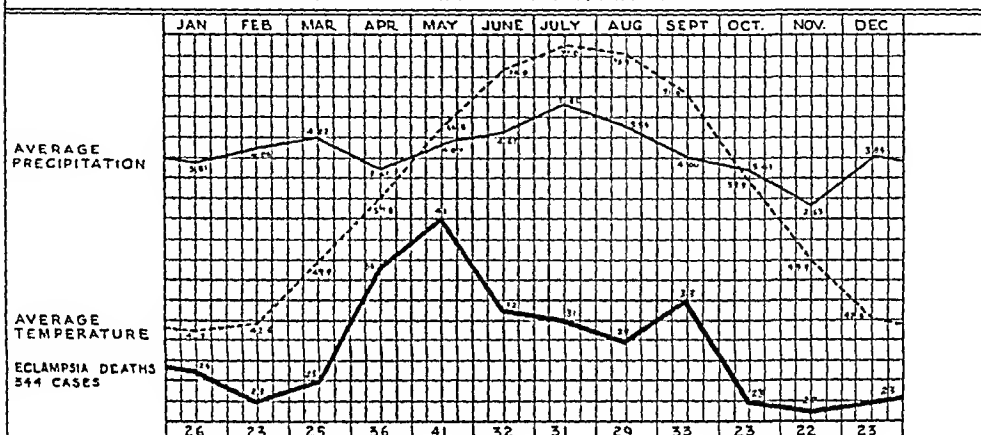


Fig. 5.

### ECLAMPSIA IN NORTH CAROLINA HOSPITALS. Duke Endowment Hospital Section.

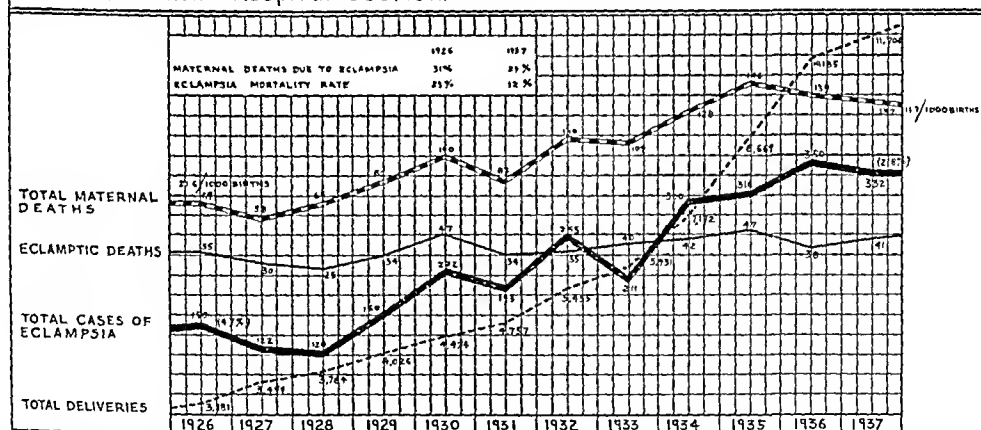


Fig. 6.

The extreme inadequacy of the medical care obtained by these convulsive cases is illustrated by the fact that 64 patients were undelivered at death and 4 were dead upon the arrival of a physician. One hundred and forty-four (42.7 per cent) were in active convulsions at the time of their first medical contact. Fifty-one were in active labor at the time of their first medical contact, and 51 had been delivered either unattended or by a midwife when a physician first arrived (Fig. 7).

Illegitimacy and race were contributing factors in the maternal mortality (Fig. 8). There were 21.8 per cent (75 cases) illegitimate pregnancies, as com-

The striking contrast of the average age in this group as compared with the fatal cases of eclampsia is revealed in Fig. 11. Thirty per cent of these patients were forty years of age or over, as compared to 17 per cent of the eclamptics (Fig. 11).

There were only 10 illegitimate pregnancies, constituting 6.4 per cent of the deaths, which is no higher than the percentage of illegitimacy in the state as a whole, and contrasts strikingly with the 21.8 per cent of illegitimacy as found in the fatal cases of eclampsia.

Race is also apparently not a factor in the nonconvulsive maternal mortality, for of the 171 maternal deaths 31.5 per cent were negroes which is no higher than the percentage of colored births in North Carolina during the past five years.

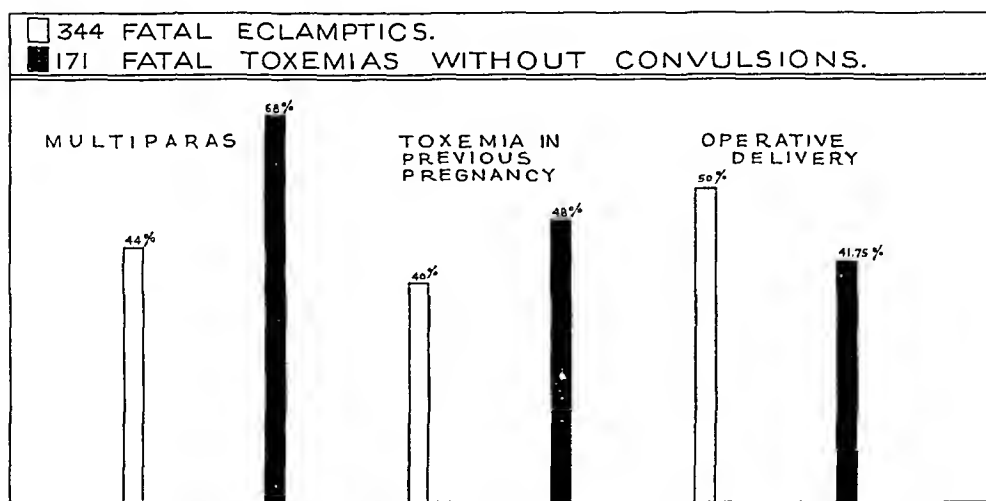


Fig. 10.

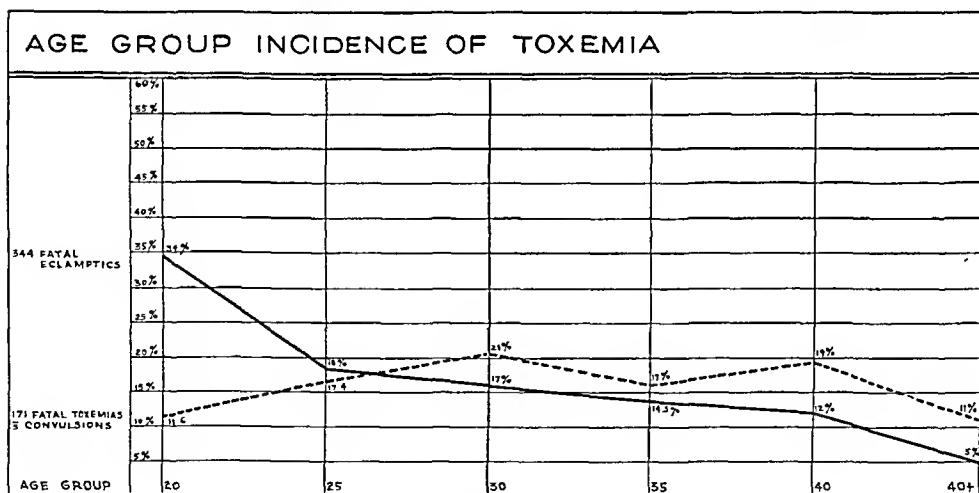


Fig. 11.

Sixty-three of these 171 nonconvulsive patients had a very acute form of hypertension, 58 had a more chronic hypertension, 7 had no hypertension, and in 43 the duration of hypertension prior to death was unknown. The amazingly high number of maternal deaths with an acute elevation of blood pressure without convulsions, coupled with the fact that in this group there were 40 deaths with acute pulmonary edema, is a striking confirmation of the fact as first reported by

The high incidence of operative interference in those patients attended by a physician prior to delivery is a condemnation of the quality of medical care. A possible trend toward conservatism is indicated by the small number of cesarean sections (10). In spite of the fact that 64 eclamptic patients died undelivered, there were 2 post-partum deliveries of living children, 1 by cesarean section and 1 by forceps.

In 27 per cent of the 344 cases of eclampsia, the onset of convulsions was after delivery. It was impossible to separate accurately the remainder into ante- and intra-partum eclamptics.

The terrific infant mortality in this group is apparent. One hundred and thirteen infants (40 per cent) were stillborn, 172 were born alive, 62 were undelivered and the fate of 11 infants was unknown. The stillbirth rate was 65.7 per 100 live births, as compared to an average incidence over the state of 4.8 per 100 live births. The addition of the 62 undelivered infants gives a fetal mortality of 101.7 per 100 live births (Fig. 8). It was impossible to analyze the additional high infant mortality from neonatal deaths.

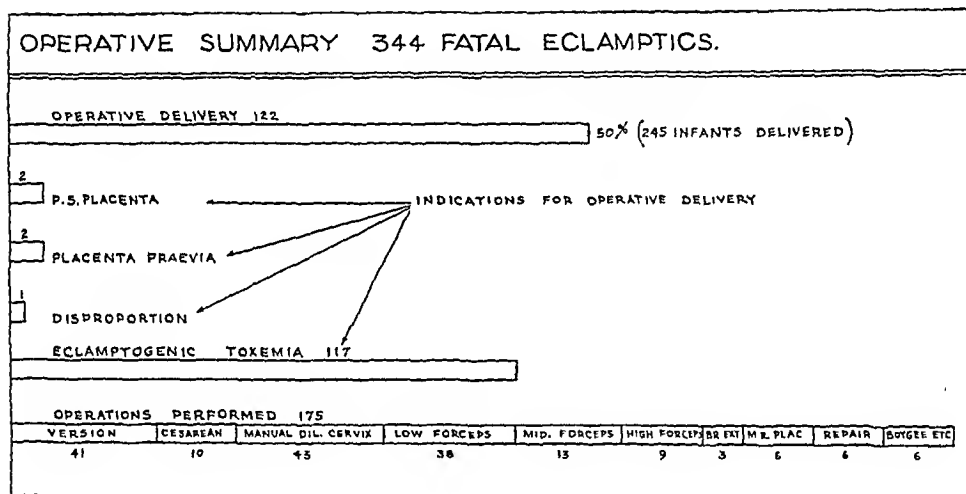


Fig. 9.

Other maternal complications include 16 cases (4.65 per cent) of twins, 9 cases of pneumonia, 3 cases of influenza, 2 cases of acute yellow atrophy of the liver, 2 cases of hyperthyroidism, 3 of diabetes, 1 of chronic mitral disease, 1 of malaria, 4 of post-partum hemorrhage, 2 of placenta previa, and 4 of premature separation of placenta.

#### 171 MATERNAL DEATHS FROM LATE PREGNANCY TOXEMIA WITHOUT CONVULSIONS IN NORTH CAROLINA

A detailed study of the 171 fatalities from late toxemias with albuminuria and/or hypertension without convulsions reveals a higher incidence of multiparity and a greater predominance of patients in the later years of the childbearing period than in the 344 fatal cases of eclampsia. The importance of a history of eclampsia or toxemia in a previous pregnancy is further emphasized in this group, as 51 (48 per cent) of the 106 multiparas gave a definite history of previous toxemia of pregnancy (Fig. 10). When the inadequacy of prenatal care and the lack of complete obstetric history in this group of patients are considered, it is quite probable that even a higher percentage of the multiparas had toxemia in a previous pregnancy.



The striking tendency toward operative interference is also present in this group of 171 nonconvulsive maternal deaths. Although 22 patients were delivered without a physician, 41 per cent of the remainder had an operative delivery. Fifty-seven operations were performed on 50 patients, consisting of 12 cesarean sections (24 per cent of all operations), 21 forceps, 10 versions, 10 surgical inductions of labor, and 4 manual dilatations of cervix. Seventy-five per cent of these deaths occurred in patients living in rural communities or in towns of less than 10,000 population. Fifty-four per cent of these deaths occurred in hospitals, as compared to 51 per cent of the fatalities from eclampsia.

There is a most striking loss of infants naturally to be expected in this group. The gross infant mortality rate (stillbirths and undelivered infants) was 110.5 per 100 live births. Thirty infants were recorded as being born alive but of less than seven months' gestation. The addition of these as neonatal deaths gives a loss of infant life of 280 per 100 live births. Only 57 of the 188 infants, including twins, are known to have had a chance for survival.

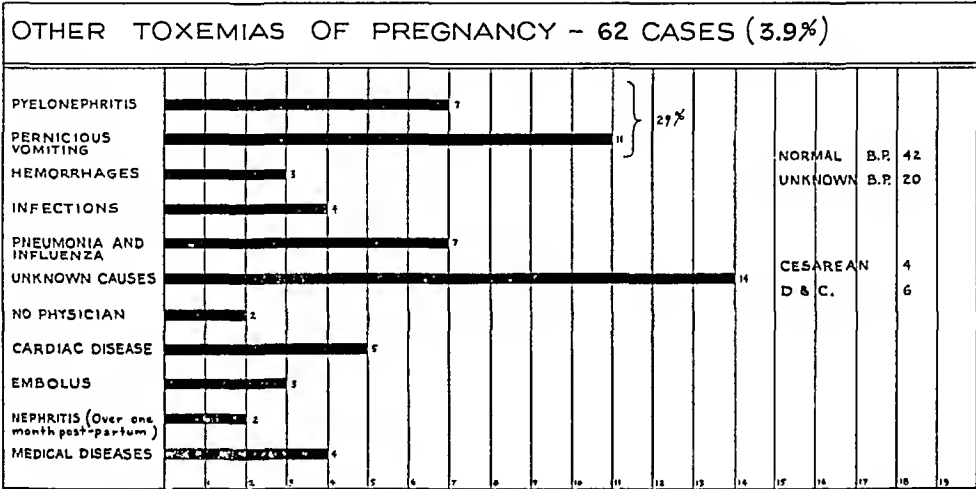


Fig. 14.

The inadequacy of medical care is also striking. Only 3.5 per cent of the 171 fatalities received competent medical supervision. In this group there was a pathetic lack of proper evaluation of physical findings on the part of the attending physician, as is shown by the fact that in 48 cases (28 per cent) prenatal care was administered by a physician who in the presence of either advanced vascular disease, gross albuminuria, or other portent physical findings, of from two weeks' to six months' duration, made no effort toward termination of the pregnancy (Fig. 13).

Lack of any prenatal care occurred as follows: 11 per cent of these patients were in labor upon the first visit of a physician, 44.5 per cent were seen for the first time by a physician late in pregnancy with gross vascular pathology, and 13 per cent received their first medical care after delivery.

62 MATERNAL DEATHS FROM "OTHER TOXEMIAS OF PREGNANCY"

An analysis of the questionnaires concerning maternal deaths classified as due to other toxemias of pregnancy (International classification No. 147) totals 62 cases which constituted 3.9 per cent of all the maternal deaths. Only a small percentage of these cases were correctly classified (Fig. 14).

There were 11 cases of pernicious vomiting of pregnancy and 7 cases of pyelonephritis, which, together, constituted 30 per cent of these maternal deaths. The remainder were found to be improperly classified, the probable causes of death being as follows: 16 (26 per cent) unknown causes, 7 pneumonia or influenza,

Teel, Reid and Hertig<sup>5</sup> that acute, pre-eclamptic toxemia may suddenly terminate in a fatal form of "cardiac asthma" without convulsions.

From the questionnaires, it appears that multiple pregnancy and pulmonary infection were additional precipitating factors in many of the deaths from acute cardiac decompensation. In the entire group of 171 nonconvulsive deaths, there were 17 cases (10 per cent) of multiple pregnancy and 9 cases (5.3 per cent) of pneumonia.

The high incidence of premature separation of the placenta (4.6 per cent) and of post-partum hemorrhage (3.3 per cent) is confirmatory of the contributing part played by vascular disease in these two conditions. The comparison of this incidence with the incidence occurring in the 344 fatal cases of eclampsia and the average obstetric incidence is shown in Fig. 12.

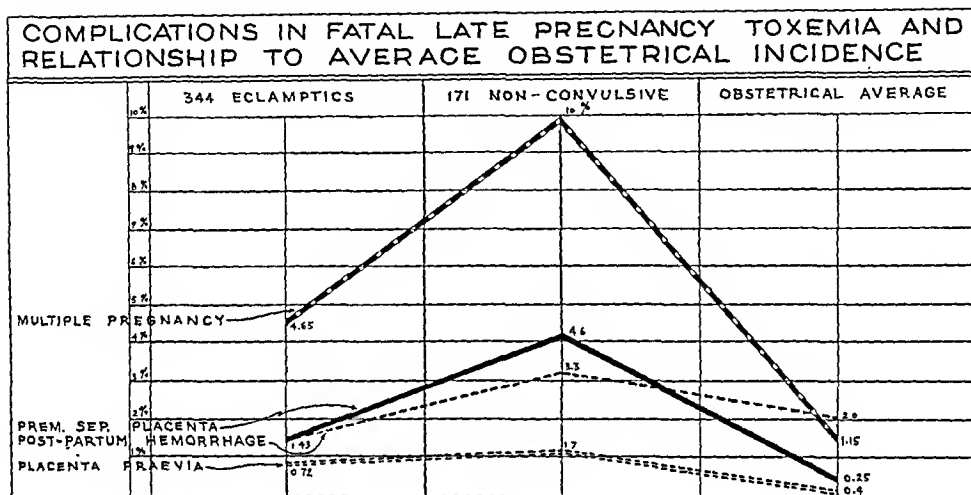


Fig. 12.

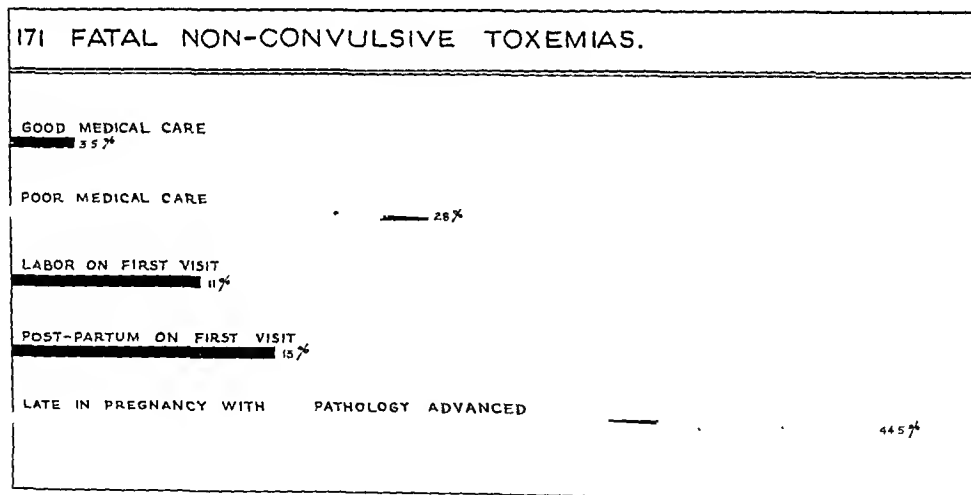


Fig. 13.

As would be expected from advanced vascular pathology, there were 15 cases of hemiplegia or cerebral hemorrhage, and one case of sudden death, probably also from cerebral hemorrhage, making a total of approximately 10 per cent of these maternal deaths due to an acute cerebral accident. There were 5 cases of uremia and 13 cases of acute nephritis. There were 2 cases of ileus. Additional complications include the following: pellagra 2, mitral disease 2, anesthesia death 1, ruptured uterus 1, inanition 1, and Vincent's angina 1.

per cent) in the nonconvulsive toxemias, the high percentage of illegitimate pregnancy in fatal eclampsia (three times the incidence of illegitimacy in the state of North Carolina) are re-emphasized.

While the incidence of operative interference upon the grave toxemia was probably unnecessarily high and hence a factor in mortality, the other extreme, namely the policy of laissez-faire or lack of early active intervention in the presence of advanced vasculorenal disease, often accompanied by a bad toxemia history, was a much more vital contributing factor to maternal mortality.

The loss of infant life needs no further comment except to repeat that the approximate yield of living viable infants from the 515 maternal fatalities was less than 40 per cent.

The increasing trend toward hospitalization of obstetric cases in North Carolina in the past decade (from 5 per cent of all births in 1926 to 20 per cent in 1937) has been accompanied by a reduction of the maternal mortality from eclampsia, which has fallen from 23 per cent in 1926 to 12 per cent in 1937.

Social and economic factors are intimately woven into the maternal welfare problem in the southern states. In North Carolina approximately 85 per cent of the state's 3½ million population are rural or live in towns of less than 10,000. Thirty-two per cent of the births are delivered by midwives and many of the remainder who are delivered by a physician are not seen until in labor.

In conclusion, it is evident that the high maternal mortality rate from toxemia of late pregnancy in the southern states as represented by this analysis of 515 such deaths in North Carolina is primarily due to social and economic circumstances. A widely scattered and rural population, a high percentage of illiteracy, the inaccessibility of adequate prenatal supervision in the past in many remote sections, the failure of prompt utilization of hospital facilities and often the inaccessibility of competent obstetric consultation, and a midwife service untrained and poorly qualified, are among the contributing factors to this problem.

The social implications necessary to cure this cancer are particularly realistic at this time. Adequate and competent maternity care for every expectant mother is a problem vitally dependent upon the active cooperation and direction of organized medical forces.

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5 cardiac disease, 4 peritonitis or post-partum infection, 3 puerperal hemorrhage unassociated with toxemia, 3 pulmonary embolus, 1 intracranial tumor, 1 post-operative psychosis, 2 acute nephritis onset over one month post partum, 1 pansinusitis and 1 amyotrophic lateral sclerosis.

There were no known cases of hypertension in this entire group. Forty-one had normal blood pressure and in 21 the blood pressure was unknown. In this group of 62 cases, there were 4 deaths following cesarean sections and 6 patients died following termination of pregnancy by curettage.

This group of deaths is reported in detail to point out the faulty deductions that may be drawn from vital statistics. In 70 per cent of these deaths, although included as due to "other toxemias of pregnancy," the patients died either of unknown causes, of medical complications, or of obstetric pathology without toxemia.

#### SUMMARY

The high maternal mortality rate in the southern states from the toxemias of late pregnancy is possibly abetted by the hot, wet climate characteristic of this section of the United States. The graph study of 344 maternal fatalities in North Carolina from eclampsia classified according to the month of death as compared to the average temperature and rainfall, confirms or rather substantiates the greater danger of this disease during the hot, wet months of the year. A similar study of precipitation and temperature in various states in the country would indicate that there is less eclampsia in the dry climate and that heavy precipitation unassociated with high temperature is less likely to be accompanied by a high toxemia rate.

A detailed study of 515 maternal deaths from late pregnancy toxemia occurring in North Carolina during the years 1932 through 1936 reveals other and more important contributing factors than those of climate. First among these is neglect. Only 12 patients received adequate prenatal care and competent medical supervision. Two hundred and fifty-two were seen for the first time by a physician late in their pregnancy, either in convulsions or with advanced toxemia. Seventy received their first medical attention when in labor, and 73 saw a physician for the first time after delivery. In 108 cases, there was prenatal care of an inadequate or faulty type.

This study confirms the fact as repeatedly stated by Stander, Acosta-Sisson, and others, that the toxic multipara with a history of toxemia in a previous pregnancy is a grave risk. Approximately 45 per cent of the multiparas in this study gave a definite history of toxemia in a previous pregnancy, a figure that is too low because of the fact that incomplete obstetric histories were obtained on many of the 515 fatalities.

This study also substantiates the additional likelihood of late pregnancy toxemia in the presence of multiple pregnancy and the increased danger in acute upper respiratory or pulmonary infections. It calls attention to the additional risk of premature separation of the placenta and post-partum hemorrhage in the toxemias of late pregnancy, because of their increased incidence as complications of the disease.

The great danger of sudden cardiac decompensation in the acute pre-eclampsias, the surprisingly high incidence of cerebral hemorrhage (10

tion of the fetus was about the only contraindication recognized. We have no hesitancy in rupturing the membranes from the seventh month of gestation, and the station of the head was not considered. A long, rigid cervix was not a contraindication.

The precise method of induction was as follows: 223 castor oil, quinine, rupture; 7 quinine and rupture; 30 rupture alone; 4 rupture, pituitary extract; 2 bag, pituitary extract, rupture; 1 castor oil and quinine; 1 castor oil and rupture; 1 rupture and bag; and 3 castor oil, quinine, bag, rupture. In the majority the patient was given castor oil, two doses of quinine (5 gr. each), a hot enema, and the membranes were ruptured later. It is difficult to prove definitely that quinine given the mother kills the baby. That it may cause congenital deafness must be considered. We are much less inclined to use the drug in pregnancy and have discontinued its use in the induction of labor. As much care was exercised in the preparation of the patient and the physician as for a vaginal hysterectomy. The puncture was made with the instruments devised by DeLee and Wilson. If the amniotic fluid did not flow freely the head was partially displaced. Metaphen was instilled into the vagina at the time of rupture and every four hours during the latent period and labor. We believe that this procedure makes such an induction safer and is, at least in part, the answer to the rather low morbidity percentage in this series. A rule of the service is to administer pituitary extract only if labor has not started eight hours after the membranes have been ruptured. As a rule, the decision to use the drug is made by the resident on duty. Two minims are given with a tuberculin syringe every thirty minutes until uterine contractions commence. Never more than six doses are given. When uterine contractions start, the drug is stopped regardless of the number of doses given. If labor does not start, the drug is repeated after twenty-four hours.

#### MORTALITY

The mortality is uncorrected. It is to be remembered that none of the women was normal and all of them were colored charity patients. The mortality was 1.9 per cent. A brief abstract of the 6 deaths is as follows: (1) Hypertensive heart disease, chronic nephritis and uremia. Attempted induction at six months. Died before labor started. The induction was probably bad judgment. (2) Eclampsia, aged 17, twin pregnancy. Died before labor started. (3) Chronic nephritis and uremia. Induction at five months. (4) Eclampsia and abruptio placentae, seven months, spontaneous delivery. (5) Eclampsia, died before labor started. (6) Eclampsia, spontaneous delivery.

#### PARITY

The pregnancy was the first for 124 of the women; 198 were multiparas.

#### AGE

Distribution as to age is shown in Table I. It is generally recognized that pre-eclampsia and eclampsia have a high incidence in young women. However, it was rather startling that the study revealed so many young women with chronic vascular disease. The incidence of this disease in colored women is probably much higher than in white women. Only 45 per cent of the women were older than 25 years.

# PREMATURE RUPTURE OF THE MEMBRANES AS A METHOD OF INDUCING LABOR\*

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ADDITIONAL responsibility is placed upon physicians who work with people lacking environmental and educational advantages. This responsibility includes the making of many major medical decisions by the physician because the patient is unable to analyze the problem.

Our obstetric clinic, all colored and entirely charity, has approximately a 30 per cent incidence of hypertensions. We experience much difficulty in correctly classifying the so-called toxemias of pregnancy. This difficulty is increased because of our crowded service and inability to keep patients long enough for final decision. We admit that the classifications as used in this study are more or less inaccurate, but they were made with all the available evidence at hand and, for practical purposes, are useful. We think it conservative to say that in our clinic we practically never see an acute nephritis as a complication of pregnancy and that proved chronic nephritis is rarer than is generally believed.

Primary vascular disease seems to be the etiologic factor in most of the sustained hypertensions during early and middle pregnancy. Pre-eclampsia as diagnosed in our clinic usually means: a hypertension developing slowly or abruptly in the last trimester of pregnancy, edema, gain in weight, certain objective symptoms and signs and, in the majority of patients, localized spastic constrictions of the retinal arterioles. Albuminuria is not a constant finding. Chronic vascular disease, on the other hand, has in the majority of cases, only a hypertension. This hypertension is usually observed much earlier in pregnancy than the hypertension of pre-eclampsia. Changes in the retinal vessels are constantly present and will be described later. Physical examination and laboratory procedures are usually negative. A practical point that will often help in the differentiation of pre-eclampsia and chronic vascular disease is that bed rest, as a rule, does not lower the blood pressure in pre-eclampsia but does lower the blood pressure in chronic vascular disease. Our clinic believes that there is no expectant treatment for a severe pre-eclampsia and that labor should always be induced.

Naturally, a clinic with such a high incidence of hypertensions will show a high percentage of labor inductions. In this paper we wish to present our results with 322 consecutive inductions in which rupture of the membranes was the basic method used. We believe that there was a definite, legitimate indication for practically every induction. Malposi-

\*Read at the First Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Charleston, S. C., February 11, 1938.

## MORBIDITY

The patient whose temperature reached 100.6° F., one or more times after the membranes were ruptured, was considered morbid. There were 47 such women, or 14.6 per cent. Twelve occurred during the latent period and/or in labor, 7 during labor and the puerperium, and 28 during the puerperium. Most were transient rises because a study of each record enabled us to classify them as follows: Sepsis 2, mild sepsis 5, and respiratory infection 1.

As has been mentioned, we believe that routine vaginal instillations of antiseptic solutions contributed materially to this low morbidity.

## COMPLICATIONS

There were no complications in 94.7 per cent of the labors (Table II). It does not seem probable that all of the complications listed can be attributed to the inductions; however, no corrections of any sort were made.

## FETAL MORTALITY

We have included in fetal mortality those babies that were stillborn as well as those who were born alive but died in the nursery. Unquestionably most of these term deaths were not caused by the inductions, but by the conditions indicating induction. However, it seems best not to attempt any corrections. The mortality rate for term babies was 4.9 per cent.

The uncorrected premature fetal mortality was 23.4 per cent. Any criticisms of this high figure should be directed against the wisdom of the judgment ordering the inductions rather than at the method.

Our clinic has long been giving maternal life every advantage over problematic fetal life.

TABLE III. CONDITION OF BABY

Term (2,500 gm. and over)		
Alive		174
Dead	4.9 per cent	9
Premature (1,500-2,500 gm.)		
Alive		90
Dead	24.4 per cent	27
Abortion (under 1,500 gm.)		
Alive		2
Dead		22

## LENGTH OF LABOR

That induction of labor by rupture of the membranes does not prolong labor seems to be shown by the fact that 87 per cent of the labors were twenty-four hours or less. As a rule, the long labors were the ones with long, irregular and ineffectual first stages. I did not see most of the women during labor and therefore cannot say accurately just how long the labor actually lasted.

## METHOD OF DELIVERY

Three hundred and seven women delivered spontaneously. The operative incidence was 4.6 per cent. There were 12 breech presentations in the series. Ten of these patients delivered spontaneously.

## PERIOD OF GESTATION

In general it is true that the nearer the woman is to term the shorter the latent period. However, there are so many exceptions both ways that a seven or eight months' pregnancy should not be a contraindication for induction by rupture of the membranes.

TABLE I. AGE DISTRIBUTION

AGE	CASES	AGE	CASES	AGE	CASES
13	2	24	11	35	6
14	5	25	13	36	11
15	7	26	11	37	5
16	14	27	18	38	5
17	21	28	11	39	3
18	23	29	14	40	5
19	20	30	11	41	1
20	17	31	6	42	3
21	10	32	9	43	2
22	15	33	13	44	1
23	20	34	9		

## INDICATIONS

Hypertensions of one sort or another were the primary reasons for the inductions in 87 per cent of the women. All indications are shown in Table II. It will be seen that 107 of the inductions were done because of chronic vascular disease. Since this work started we have become a bit more conservative as regards essential hypertension. When the diagnosis is made in early pregnancy and the hypertension is severe, we think the pregnancy should be terminated and the woman sterilized. When the diagnosis is made at the fifth or sixth month and there are no evidences of heart failure, kidney damage, or superimposed true toxemia, we wait until we are sure of viability, induce labor and sterilize later.

It seems worthy of mention that in eclampsia every attempt is made to control the convulsions before the induction is started.

TABLE II. COMPLICATIONS

305	None
8	Postpartum hemorrhage
2	Prolapsed cord
1	Prolapsed arm
2	Retention piece of placenta
1	Placenta previa
2	Abruptio placentae
1	Dystocia

## METHOD OF INDUCTION

Rupture of the membranes was the basic procedure used. One medical induction is included through error.

## THE LATENT PERIOD

The latent period was less than twenty-four hours in 86 per cent of the labors. Inductions with such latent periods rarely occasion anxiety. It is the approximate 14 per cent with more or less long latent periods that cause us concern. When one decides to induce labor by rupture of the membranes, all bridges are burned; one's steps cannot be retraced. If the latent period remains fever free, its length causes little worry. As will be discussed under morbidity, only 47 women in the series had as much as a single rise of temperature to 100.6° F. It is believed that the routine instillation of metaphen into the vagina was in large measure, responsible for the low incidence of fever. When we figure that 51 per cent of the women had reached only the eighth month of gestation or less, it is not surprising that there were so many long latent periods. A woman at term is far more likely to have a shorter latent period than one at eight months. However, there are surprises either way.



## THE RELATIONSHIP OF THE TIME OF LIGATION OF THE CORD TO THE RED BLOOD COUNT OF THE INFANT\*

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TARNIER taught that to tie the cord at once deprived the infant of the blood that was left in the engorged placenta, which with more patience would have returned to the body of the infant.

To give some experimental support to his master's teaching, Budin measured the blood that flowed out of the umbilical vessels when the cord was cut at varying intervals of time. In 32 cases the cord was not tied until pulsation had ceased. The umbilical vessels pulsed from one-half to fifteen minutes, with an average time of two and one-fourth minutes. The average amount of blood that flowed out of the cord was 11.2 c.c. In 30 cases in which the cord was ligated at once the average amount of blood collected was 98.4 c.c. In 13 cases in which there was a delay in tying the cord of from one and three-fourths to seven minutes, but in which the cord was still pulsating, the average amount of blood from the cord was 41.46 c.c. Schückling, writing two years later (1877), called this blood "reserve blood." It is used, he said, to fill the pulmonary vessels when they expand. He demonstrated an increase in the babies' weight of from 30 to 110 gm. when the umbilical cord is not clamped. The babies whose cords were tied immediately had a more rapid pulse and gained weight more slowly. Whereas those whose cords were tied late had a slower pulse and regained their birth weight in four to six days. The latter group had no jaundice. This is at variance with the only recent article we have seen on the subject, Franklin noting a higher percentage of jaundice in the babies whose cords were tied late. Hazelhorst not only weighed the babies before and after the cord stopped pulsating, but recorded the weight change graphically by attaching a writing point to the beam of the balance. In some cases where there were strong pulsations of the umbilical vessels there was a loss in weight at first, but an ultimate gain as the vessels ceased pulsating. The average gain in 20 cases was 114 gm. The greatest gain took place in the first few minutes. Uterine contractions caused a gain in weight of the baby.

For a number of years one of us has noticed a marked variation in the number of red blood cells of the newborn infant. Apparently neither the method of delivery nor the type of anesthetic had anything to do with it. The present study was undertaken in hopes of throwing some light on this subject. We repeated Schückling's experiment of weighing the baby immediately and after the cord ceased pulsating. It was easy to demonstrate a definite gain in weight when the cord ceased to pulsate.

In upwards of 400 unselected cases the umbilical cord was tied at varying intervals from one to fifty minutes. The patients were white private patients. All had sodium amytal scopolamine analgesia and ether anesthesia. It is interesting to note that the cord continued to pulsate longer than in Budin's series where probably no anesthesia was used. In one instance pulsations continued for fifty minutes. The amount of blood that drained out of the placental end of the cord was measured.

\*Read at the Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Charleston, S. C., February 11, 1939.

## EYE GROUND EXAMINATION

Ophthalmoscopic study was done 231 times. Positive pathology was determined in 82.7 per cent of the women studied. That practically all of the examinations were done by one man increases the value of the results. Hallum and Bartholomew have done much work along this line in our clinic, and I am quoting at length from their report because of the great practical importance of the procedure:

"The necessity for induction of labor arises most frequently in connection with toxemia of pregnancy. It is therefore important to know if the toxemia is of the more urgent preeclamptic type and, if so, how long one may safely temporize before terminating the pregnancy.

"Without minimizing the importance of the blood pressure, urine examinations or clinical symptoms, the ophthalmoscopic findings should be considered of great value in answering the above questions.

"If hypertension has existed since the early months of pregnancy, the condition is probably that of chronic vascular disease. The arteries appear pale, the light reflex or arterial stripe is definitely increased, and there is a disturbance in arterio-venous ratio from a normal of 2 to 3 up to 1 to 2, 3 or 4. Slight irregularities in caliber may be found but arterial spasms are rarely seen. Due to sclerosis of the arterial wall there is a distinct arterio-venous compression where an artery crosses a vein, with dilation of the vein, distal to the compression. If one sees yellow-white exudates or cotton-wool patches, there is probably an associated chronic nephritis.

"If hypertension arises late in pregnancy, the condition is usually one of true toxemia of pregnancy, which may progress to preeclampsia or eclampsia. The A.V. ratio is normal and there is no increase in light reflex, and no A.V. compression. Within a radius of two or three disc diameters of the disc, one may find one or more sharply localized arterial spasms. With further increase in toxemia, the spasms become spindle-shaped and finally lengthen until the whole artery becomes constricted. At this stage it may simulate chronic vascular disease except for the associated severe toxic symptoms and findings. Marked edema of the retina and hemorrhages may be seen in the preeclamptic or eclamptic stage."

## COMMENT

It is probably true that we are more justified in sanely temporizing with intelligent private patients on a good economic level. However, I think this is often overdone. I still think that too great value is placed upon problematic fetal life and the mother subjected to unwarranted risks in its name. Often, too, is this not the excuse for lacking the courage of our convictions and the will to proceed with a disagreeable task?

In the light of our present knowledge I do not believe that we can tell just what is the influence of conservative treatment of the true toxemias upon subsequent hypertension and chronic nephritis. It is perhaps greater than we realize at the present time. Pregnant hypertensive women with one or more living children deserve humane as well as religious consideration.

In conclusion, I believe that I am justified in making one positive statement. The greatest factor in differentiating the various hypertensions of pregnancy is a prolonged period of observation.

3. In infants whose umbilical vessels are ligated after they have ceased to pulsate, the average red blood cell count is greater by 584,481 than in those whose cords are ligated while still pulsating.

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MEDICAL ARTS BUILDING.

### PELVIC INLET VARIATION IN 400 NEGRO WOMEN\*

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THE modern classification of the female pelvis which has been developed slowly during the past 100 years has culminated in the work of Caldwell and Moloy<sup>1</sup> and Thoms,<sup>2</sup> and others.

It has been shown that external measurements of the pelvis bear little relation to the internal measurements. The external conjugate, considered to be the most reliable of these, may be very inaccurate as an index to the conjugata vera as shown in a recently examined case of an achondroplastic dwarf whose Baudelocque measurement was 17. The conjugata vera as determined by internal measurement and confirmed by the grid method of roentgen pelvimetry was 6 cm.

In fact, external pelvimetry is of so little value that we believe the time has come when it can be discarded. The estimate of the constitutional type of the patient is of far greater value in prognosis of labor. Women of slender and medium constitutions as a rule do well. Those giving most trouble in labor are the overweight, heavy-featured type, with male distribution of hair. These are inclined toward the Froehlich type, the dystrophia dystocia syndrome described by Horner<sup>3</sup> and, in addition to a tendency to possession of rarer types of pelvis and a predilection for occipitoposterior presentation of the fetal head, have painful but ineffective uterine contractions, possibly associated with hormonal disturbances. Of all methods of study of the obstetric pelvis short of roentgenography, the most valuable is estimation of the conjugata vera by subtracting 1½ to 2 cm. from the measured conjugata diagonalis. Criticism has been made that the promontory cannot be palpated in all patients. When that occurs the diameter is usually large enough. In all cases of contraction in which the conjugata vera was 9 cm. or less, we have been able to estimate it within 0.5 to 1 cm. as checked by the x-ray "grid" method. Palpation of the contour of the ischial spines and the subpubic angle gives a fairly good estimate of the outlet.

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A blood count was made by the hospital technician within twenty-four to thirty-six hours. The infant's red blood cells varied from 3,280,000 to 7,120,000. In 59 cases in which the cord had ceased to pulsate before it was tied, the infant's red blood cell count averaged 5,783,400, whereas in 333 cases in which the cord was pulsating when tied the red blood count averaged 5,198,919, a difference of 584,481.

We have plotted 400 cases in relation to the time of tying the cord and the infant's red blood cells in millions. Apparently there is little if any correlation. The coefficient of correlation worked out by Pearson's formula is +0.105 and the probable error is  $\pm 0.0329$ . The correlation is positive but not significant as it is only three times the probable error.

We also have plotted 400 cases in relation to the time of tying the cord and the amount of blood left in the cord and placental vessels. Here too there is apparently little correlation. However, the coefficient is  $-0.2564$ . The probable error is  $\pm 0.0315$ . As the coefficient is more than six times the probable error it is significant.

The cases were likewise plotted in relation to the infant's red blood cells in millions and the amount of blood left in the cord vessels in cubic centimeters. Here there is apparently some negative correlation. The coefficient of correlation is  $-0.36$  and the probable error is  $\pm 0.0293$ . The correlation is not great, but as it is more than twelve times the probable error it is significant.

#### DISCUSSION

There is practically no correlation between the number of minutes that elapse before the cord is ligated and the red blood cell count of the infant. One factor that does not show in these figures is the cessation of pulsation. If a cord be watched immediately after delivery the umbilical vessels can be seen to pulsate strongly throughout their entire length. In a varying length of time the pulsations cease in the more distal part and as this occurs the umbilical vessels collapse. This process of cessation of pulsation and collapse of the vessels proceeds toward the umbilicus until finally there is no pulsation even at the navel. The vessels are then entirely collapsed. If now the cord be tied and cut very little blood will escape from the placental end. The cord may cease pulsating at any time, sometimes even before the baby is born. There may be other factors involved, but certainly the length of time before tying the cord *per se* has no influence on the amount of blood left in the umbilical vessels.

On the other hand there is a significant negative correlation between the amount of blood that is left in the umbilical vessels and the number of red blood cells in the infant's circulation. This is also shown by higher red blood cell count of those infants whose cords were allowed to stop pulsating before they were ligated. Here too there are probably other factors. This factor, however, is significant enough to justify waiting until the cord ceases to pulsate and the umbilical vessels collapse especially in small and premature infants.

#### CONCLUSIONS

1. The less blood that is left in the umbilical vessels the higher will be the red blood cell count of the infant.

2. If the umbilical vessels are allowed to cease pulsating and collapse before they are ligated, very little blood will drain out of them.

groups of Caldwell, Moloy and D'Esopo,<sup>5</sup> gynecoid (female type), anthropoid (ape or fetal type), android (male type) and platypelloid (flat pelvis type). However, many cases overlap, so that characteristics of two or possibly more of the groups occur in the same pelvis. Caldwell and others have taken care of this by subgroups which they illustrate. In order to correlate this study in regard to colored women with theirs in white women, we have consulted their drawings of the various subtypes and have taken the liberty to group them all under the four main heads. In their 215 white women then, what we would classify as gynecoid occurred in 58.5 per cent, anthropoid 18.1 per cent, android 22.2 per cent, and platypelloid 0.9 per cent.

Our classification of the negro pelvis by the same standards is, gynecoid 60.25 per cent, anthropoid 31 per cent, android 6.75 per cent and platypelloid 2 per cent. In this classification the principal difference between the two races lay in 80 per cent more anthropoid and more platypelloid types and less than one-half as many android types in the negro in comparison with the white women. Table I shows the number of cases in each group with the different lengths of the conjugata vera. The majority fall into the group with conjugata vera of 10 to 11 cm. Thoms has a somewhat similar classification but it seems to exclude the male type pelvis and is based more on the relation between the antero-posterior and transverse diameters as revealed by the "grid" method of roentgen pelvimetry. This work on the negro pelvis however bears out his contention that the average normal female pelvis is essentially

TABLE I

<i>Gynecoid</i>					
CV in cm.	8½	9	10	11	12
Cases	1	30	111	90	9
<i>Anthropoid</i>					
CV in cm.	9	10	11	12	13
Cases	1	22	64	29	8
<i>Android</i>					
CV in cm.	9	10	11	12	
Cases	3	14	9	1	
<i>Platypelloid</i>					
CV in cm.	6	7	8	9	10
Cases	2	2	1	2	1

TABLE II\*

	WHITE 100 NURSE	132 CLINIC	450 CLINIC	107 CHILDREN	400 NEGRO WOMEN TORPIN
Dolichopellic	37	14.6	15.5	57.9	9.25
Mesatipellic	46	43.9	45.1	33.6	36.50
Brachypellic	17	34.1	34.5	8.3	49.75
Platypellic	0	8.3	4.9	0.0	4.50

\*NOTE: Thoms' chart of classification of white female pelvises are shown in the first four columns. The fifth column incorporates the 400 negro female pelvises of this study grouped according to Thoms' classification.

This study of 400 negro female pelves, made entirely upon the dimensions and outline of the superior strait, was associated with the use of a device previously described<sup>4</sup> for simplifying Thoms' method of roentgenpelmimetry with which we routinely use an 8 by 10 inch film. Most of these patients were not pregnant. Many were pregnant and some in the first stage of labor. They were studied as far as possible in conformity with published studies on series of white women. As a rule the contours of the inlet allow fairly definite classification as to the four

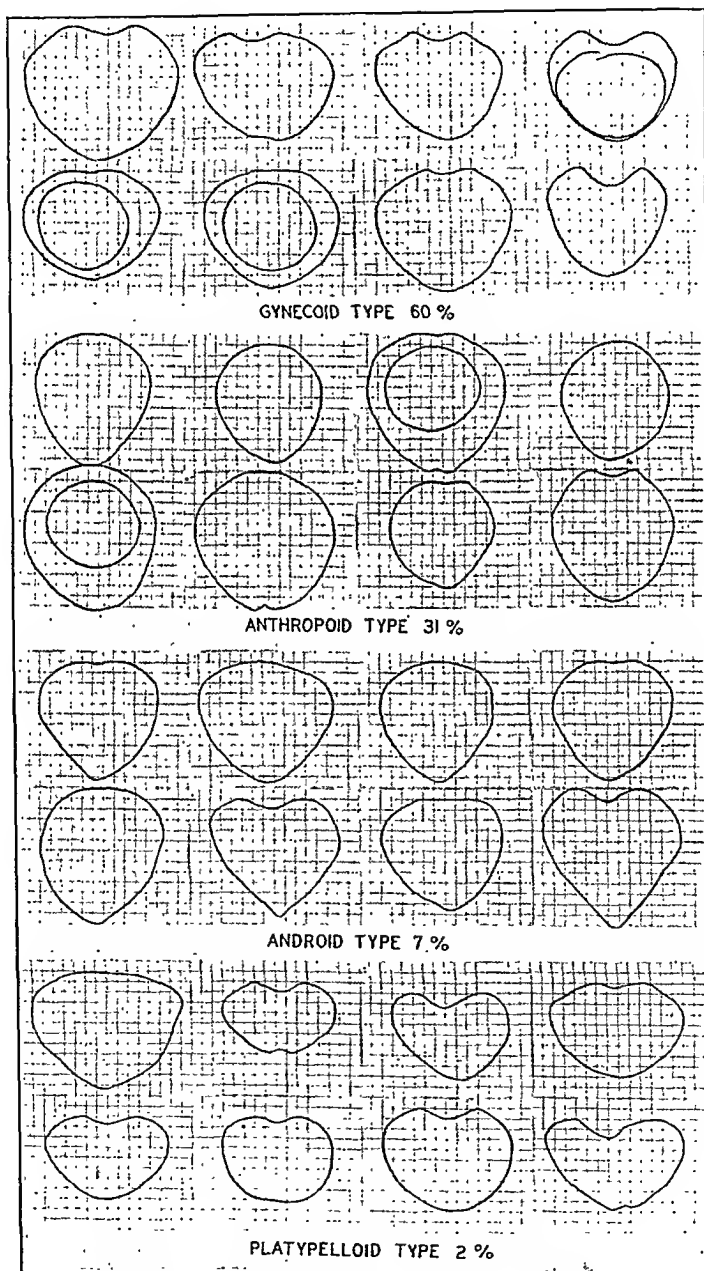


Fig. 1.—Chart showing actual outlines, drawn to centimeter scale, of individual pelvic inlets from the group of 400 negro female pelves. The incidence of each of the 4 types is stated.

with large fetuses. The forward jutting promontory was noted in the film of the superior strait and was demonstrated at the operation in each case.

#### SUMMARY

1. Study of the superior strait in 400 negro female pelves by Thoms' grid method revealed more anthropoid and less android types of pelves than occur in the white patients as studied by Caldwell and others.

2. A device is illustrated (Fig. 2) for simplifying Thoms' grid method so that the superior strait may be viewed and measured from an 8 by 10 inch film and a technician may complete the procedure in ten minutes.

3. The inlet to the majority of negro female pelves is essentially round in agreement with Thoms' findings in white women.

4. The operative incidence of the negro women may be less than in the whites partially because of less occurrence of android type of pelves.

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## ENDOMETRIOSIS OF ROUND LIGAMENT WITH REPORT OF CASE\*

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**E**NDOMETRIOSIS of the round ligament is a rather rare condition and that is the reason for the report of this case.

Mrs. T. J., aged 29 years, weight 126 pounds, reported to me on Aug. 3, 1938, complaining of pain in right groin. The pain had been present for last nine years; for the past six years, she had noticed a small nodule in right inguinal region, which was painful; on pressure, the pain radiated into the lower right quadrant; the pain was worse at night and frequently the patient could not sleep due to pain in the right inguinal region. The symptoms were increased during the menstrual period.

This patient had been married ten years. There had been no pregnancies, although no contraceptives had been used. Mother died at the age of 58 years of carcinoma of fundus of uterus. Father died at the age of 63 years of angina pectoris.

In 1931, seven days before menstrual period was due, patient had an attack of lower right quadrant pain. She had an appendectomy done at midnight and was told by the surgeon that her appendix was not bad. Her convalescence from the appendectomy was normal. She remained in the hospital for ten days.

This patient had had the usual childhood diseases, no serious illnesses. Menses began at 11 years, regular every 28 days, lasting 5 days. No pain except in right inguinal region. The Wassermann reaction was negative, hemoglobin, 85; red blood count, 4,830,000; white blood count, 6800; leucocytes, 68; lymphocytes, 26; monocytes, 4, and eosinophiles, 2; urine, negative.

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round, inasmuch as 64 per cent of them appeared to be essentially round to the casual observer and, in fact, the radii in any such case varied no more than  $\frac{1}{2}$  cm. in length. Table II compares the group with that of Thoms.

Thoms records the delivery of the 600 white patients studied. There were 15 cesarean sections, 76 low forceps, 18 midforceps, and 4 version and extraction operations performed. While we have no record on these particular 400 colored patients, our operative incidence on this class of patients is about as follows: Cesarean operation once in about 200 cases and forceps, low and mid, about  $2\frac{1}{2}$  per hundred deliveries. McCord (personal communication) has even a lower operative incidence. "In 600 consecutive deliveries, all colored patients, there were 2 cesarean, 9 low forceps and 1 midforceps operation."

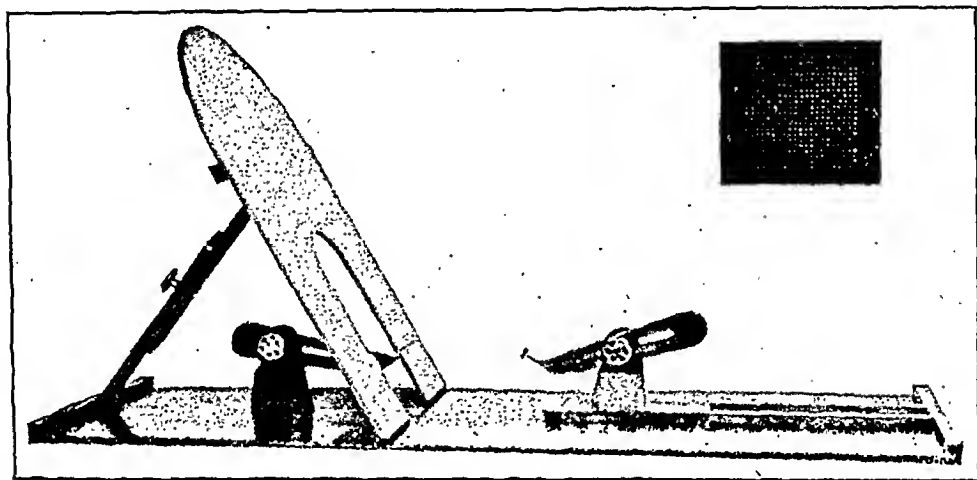


Fig. 2.

It may be added that in the series of 400 pelves reviewed, there were 3 cases which were sent from other clinics merely because of the extreme degree of contraction. One of these was a dwarf whose conjugata vera was 6 cm. This unduly increases our platypelloid group.

In this study most of the films were quite readily classified into the four groups, gynecoid, anthropoid, android, and platypelloid, but there was one feature of the superior strait not discussed by recent writers and that is a forward placed promontory jutting out into the posterior aspect of the superior strait. No note was made of this unless it extended 1 cm. or more. This occurred in 10 per cent of the series,  $9\frac{1}{2}$  per cent of the gynecoid, 7 per cent of the anthropoid, 15 per cent of the android, and 62 per cent of the platypelloid. Consequently this is an important factor in the estimation of each patient's ability to deliver, especially when the type of the pelvis is platypelloid, android or gynecoid. It was the determining factor in two recent cesarean operations after prolonged test of labor in gynecoid pelves of small dimensions,



## CURRENT VIEWS ON THE CAUSATION OF MENSTRUATION\*

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THE modern phase of studies on the menstrual cycle began seventeen years ago when Corner began observing the menstrual cycle of the monkey. Following the lead of Corner, Edgar Allen used the newly discovered estrogenic hormone on ovariectomized monkeys and first stated his belief that menstruation was caused by withdrawal of estrogen, which has been elsewhere called the estrin deprivation theory.

A brief recapitulation of the stages which permit our present interpretation of the role of the sex hormones is necessary, although the details are familiar to many. The first experimental observations were those of Allen, which were the basis for the estrin withdrawal theory which he and many other observers still maintain. There is no doubt that withdrawal or reduction of the estrogen level by any means results in typical uterine bleeding. The high incidence of anovulatory menstrual cycles in the monkey, especially those in captivity, makes this animal an excellent form for those who would elaborate and justify this theory. So in all of these experiments, the bleeding which followed estrogen withdrawal is a result of the breakdown of a proliferative endometrium. This phenomenon of uterine bleeding after withdrawal of estrogen can best be summarized graphically (Fig. 1).

The bleeding threshold to estrogen withdrawal has been approximated by Zuckerman<sup>1</sup> from a large series of observations. He determined that the amount of oil used as a vehicle for injection is of no significance, and that dosage per day, whether 0.03 mg., 0.1 mg. or 1.0 mg., made little difference in the latent interval between withdrawal of the hormone and bleeding. Zuckerman<sup>2</sup> injected spayed animals with a standard amount of estrogen which, in individual cases, ranged from 400 I.U. daily to 5000 I.U. daily for fourteen days. When this dose was reduced in varying amounts and percentages, a bleeding threshold to estrogen was determined. Thus, the dosage to which such pretreatments could be reduced without permitting bleeding was found to be not below 250 I.U. daily. Below this level, that is, between 150 I.U. and 250 I.U., lies the threshold for bleeding in which some animals will bleed. Zuckerman suggests that 200 I.U. may be taken as a uterine threshold for most monkeys.

The other point of interest here is that the percentage of reduction which is made in lowering the dose is of no significance. That is, the treatment may be at 400 I.U. per day or 5,000 I.U. per day. Uterine

\*The previously unpublished data here presented were aided by a grant from the Rockefeller Foundation.

General physical examination negative except for a small tender mass in right inguinal region about 3.5 by 2.5 cm in size. This mass was lying over the pubic bone and apparently was attached to it. X-ray examination revealed no bony pathology.

On return visit, the small mass was manipulated and the patient complained of severe pain. After a week, the pain gradually subsided, although the mass was still tender, but on subsequent visit the mass was found to be mobile.

Pelvic examination was negative.

On Aug. 28, 1938, a right inguinal incision was made extending from the canal of Nuck to symphysis. The nodule was explored and removed and the mass was found to be a continuation of round ligament. The ligament was removed high in the canal and transfixed.

The following is the pathologic report by Dr. Kenneth M. Lynch: "Received a somewhat rectangular piece of tissue measuring approximately 3.5 by 1 cm. in diameter. The surface is covered by a rough, thin, whitish gray membrane. Section reveals a white fibrouslike center. Also received a small irregular sheetlike piece of tissue measuring 1 cm. in greater diameter and containing 2 catgut sutures.

"Two sections of tissue, one containing muscle and showing serous membrane covering on one side. The other is of more dense connective tissue and containing islands of cellular stroma resembling that of the endometrium, enclosing channels, lined by columnar ciliated type epithelium, containing blood and granular debris."

Diagnosis: *Endometriosis of round ligament.*

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In earlier work we<sup>4</sup> showed that the bleeding of estrogen deprivation did not occur if the estrogen were replaced by progesterone. After a course of progesterone, bleeding always occurred after the withdrawal of progesterone.

The same series of experiments<sup>5</sup> also demonstrated that this bleeding was not prevented by following the progestin by doses of estrogen several times larger than would effectively prevent bleeding without the progesterone treatment. These observations were confirmed by Hisaw and his associates, and by Corner on the monkey, and by Kaufman and many others for women.

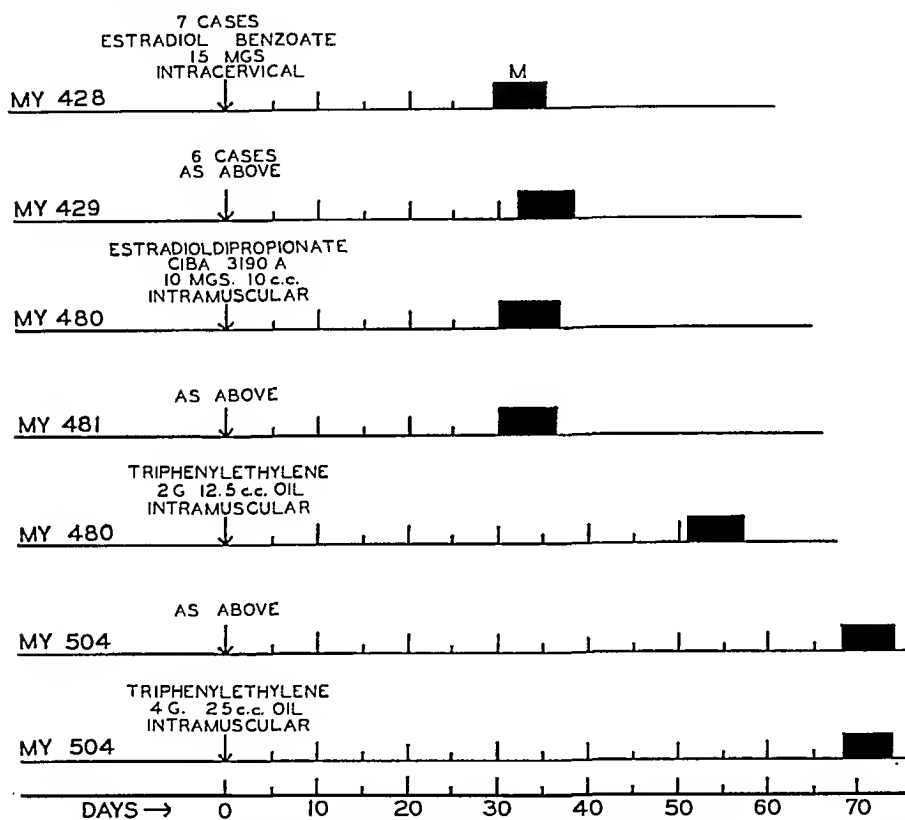


Fig. 2.—Graph showing latent period for uterine bleeding in days after a single injection of various estrogens.

These experiments on monkeys and women merely established that which was already believed from clinical and pathologic experience, viz., that the histologic sequences of the menstrual cycle were induced by the ovarian hormones, and that menstrual bleeding from a gravid endometrium followed cessation of progesterone action on the endometrium.

The character and duration of the bleeding resulting from withdrawal of either hormone are the same. The time interval between hormone withdrawal and bleeding, however, is characteristic for each hormone.<sup>6</sup> The time of onset of bleeding after estrogen withdrawal is 9.2 days, with a range of five to sixteen days. After cessation of progesterone treatment, however, bleeding occurs on an average of 2.9 days, with a range of two

bleeding will occur only if the estrogen level is reduced to the threshold zone, approximately 200 I.U. for the rhesus monkey. This would signify a drop of 50 per cent or of 4 per cent but bleeding occurs only within the threshold zone.

The course of action of a single injection of various estrogens was followed in a small series of animals (Engle and Crafts<sup>3</sup>).

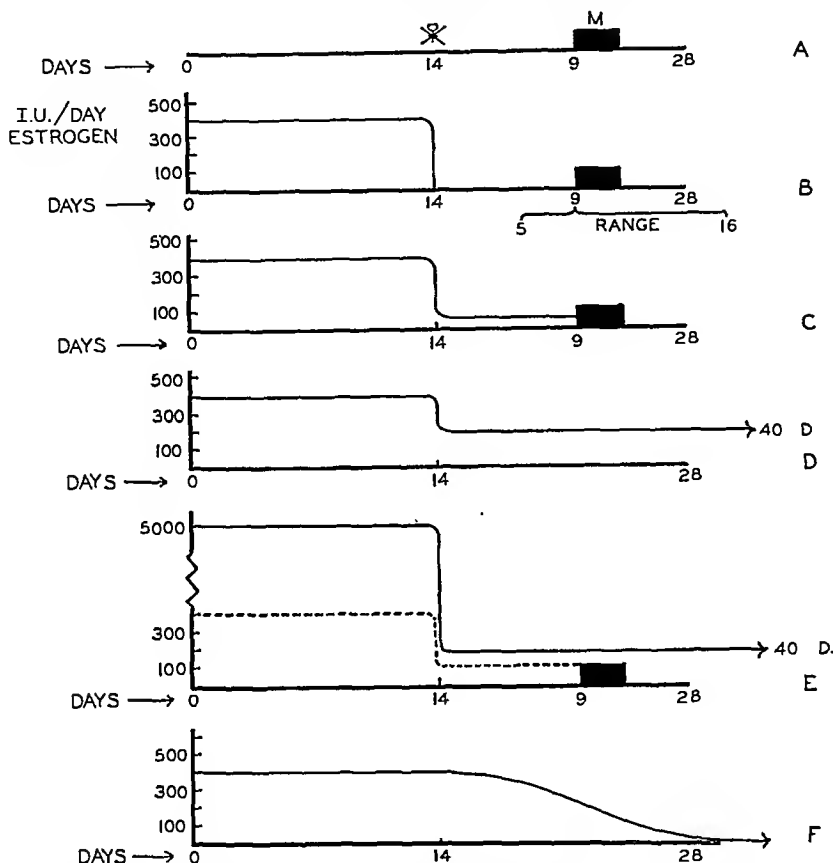


Fig. 1.—Estrogen-threshold and uterine bleeding, showing observations made over a period of years by a number of investigators, and which have become common experience among workers in the field of experimental menstruation in monkeys. A, Estrogen withdrawal by means of castration only in adolescent or adult animal, not in infants or juveniles. B, Cessation of injections of estrogen. C, Bleeding will occur if the amount of available estrogen is reduced below the endometrial threshold. D, Bleeding can be prevented for variable periods of time even though the amount is reduced, provided it is above the threshold level. E, The quantity of estrogen originally given is not a factor, neither is the percentage of reduction of estrogen, nor is the amount of oil used as a vehicle important, provided that the endometrial threshold is exceeded (Zuckerman). F, Involution of the endometrium may occur without bleeding by the gradual reduction of estrogen (Hisaw).

A single injection in an area where slow absorption of the oily vehicle might be expected showed that the bleeding would appear on the thirtieth to the seventieth day after the single injection (Fig. 2).

An attempt has been made to present the evidence to date regarding the conditions under which the withdrawal of estrogenic hormones is followed by bleeding. It is, however, obvious that, interesting as the observations may be, they do not explain the role of estrogens in the ovulatory menstruation of the normal adult woman.

that estrogen and progesterone were not antagonistic in their action on the monkey endometrium, but were essentially synergistic.

In these observations, we were interested in structural changes of the endometrium, and presented some evidence that estrogen and progesterone might act together in preparing a gravid endometrium. Similar studies on the human being have not been reported, but these experiments were designed to repeat the conditions of hormone balance and action, believed to be true in the human menstrual cycle.

Attempts to analyze the endocrine factors involved in menstruation have involved the adrenals, thyroids, and the anterior and posterior pituitary glands. All attempts to demonstrate direct participation of these hormones in the bleeding process have been negative.

The anterior hypophysis participates indirectly in the menstrual cycle, but the work of Philip Smith shows so clearly that the bleeding response to estrogens and to progesterone is not greatly changed in completely hypophysectomized monkeys. Direct action of the pressor principle of the posterior hypophysis also appears to be without effect on the bleeding response.

Thus, the experimental trend has returned to the task of determining the respective roles of estrogens and progesterone withdrawal in the bleeding response.

There is now no controversy over the relationship of progesterone to the latter half of natural or experimental cycles. The bleeding of estrogen withdrawal is invariably prevented if progesterone is administered. In normal nonovulatory or ovulatory cycles, progesterone administration will inhibit menstruation for the duration of the treatment. Estrogen administered in the latter half of an ovulatory cycle in monkeys or woman has no effect on the time of appearance of the menses. Bleeding follows cessation of progesterone administration, even though very large quantities of estrogens are given. General agreement exists among the workers with monkeys as to the validity of these facts. Recognizing these experimentally observed facts on the immediate role of progesterone in inhibiting bleeding, Corner<sup>10</sup> has made "the assumption that progestin acts to prevent estrin from protecting the endometrium against bleeding."

In his experiments where estrogen and progesterone were given concurrently, it requires much more estrogen than the combined "bleeding prevention" values of the two substances to inhibit bleeding after the cessation of the two.

Corner<sup>10</sup> found that 125 I.U. of estrogen per day for ten days would be followed by bleeding on withdrawal. The threshold value of progesterone for bleeding inhibition was about 0.5 mg. By combining the two substances he obtained a "bleeding prevention" value of 325 to 425 I.U. of estrogen. However, after cessation of these combined injections he found that the bleeding prevention value needed was about 750 units. From these data Corner derives his thesis that progesterone suppresses the menstrual inhibiting value of the estrogen. He believes that the "significant action of the progestin has been to create, by depressing the action of estrin, a state equivalent to estrin deprivation."

to four days. Thus, while the latent period before bleeding after estrogen withdrawal is quite long, and the variability great, it is very brief and constant after progesterone withdrawal (Fig. 3).

These observations have been made by given periods of injection with estrogen or with progesterone. In attempting to reproduce the hormonal regulation of the human menstrual cycle, however, it could not be

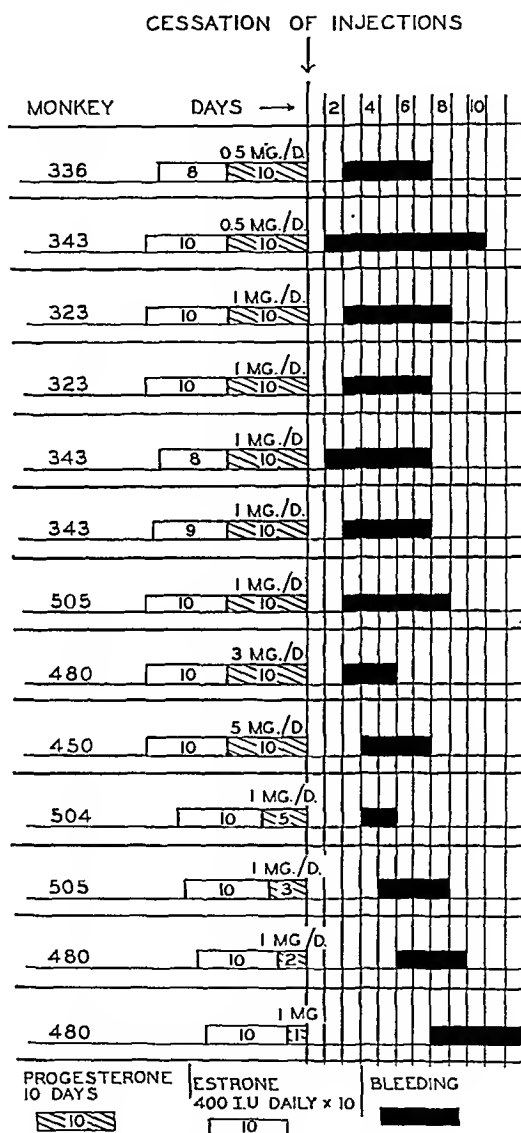


Fig. 3.—Graph showing the latent period for uterine bleeding in days after progesterone withdrawal.

thought that there was any such sharply demarked line of separation between the two. That is, no one could consider that the action of estrogen stopped suddenly at the hour of ovulation. Indeed, all data available indicate that estrogen was present, and was probably continually being produced by the follicles or the corpora lutea during the entire cycle. Experiments of our own,<sup>8</sup> as well as those of Hisaw and Greep,<sup>9</sup> indicated

the progesterone, even for twenty days, without bleeding or involution or loss of the secretory character. These experiments are not comparable to the reports on suppression of menstruation in woman with intact ovaries.

In reporting these experiments no explanation is offered as to the physiologic or chemical factors involved in these two diverse effects obtained with the same chemical agent.

In an ovariectomized monkey which has been permitted to bleed, the endometrium after regeneration is the usual thin, sparsely glandular endometrium of castrate atrophy. In such an animal 25 mg. of testosterone daily will cause considerable growth of the endometrium with a high columnar epithelium, but rather dense stroma. The histologic effect of testosterone alone does not completely develop the proliferative phase induced by an estrogen only.

When testosterone is withdrawn, a long latent period of fifteen to twenty-five days occurs before bleeding, which equals or exceeds the longest period of latency obtained with estrogen withdrawal.

Regeneration of the endometrium of an ovariectomized monkey after bleeding may be caused by crude progestin only.<sup>12</sup> Such a degree of endometrial growth as Hisaw reported has not been produced by us with crystalline progesterone (Proluton, Schering). Covering of the denuded surface of the endometrium will, of course, occur in the absence of the ovaries or any hormone administration.

Though there is an endometrial growth and proliferation, uterine bleeding has not occurred after the progesterone withdrawal. Dosages up to 5 mg. of progesterone per day, with no pretreatment with estrogen, cause slight endometrial growth, but bleeding does not occur after cessation of such treatment. (Table I.) Zuckerman<sup>13</sup> reported no bleeding after fourteen days' treatment with 2 mg. of progesterone daily.

TABLE I. NO BLEEDING AFTER PROGESTERONE ONLY

MONKEY	DAYS SINCE LMP*	PROGESTERONE DAILY MG.	NUMBER OF DAYS INJECTION	OBSERVED AFTER LAST INJECTION	REMARKS
462	10	2½	14	No bleeding in 24 days	
462	--	5	14 Biopsy day 15	No bleeding in 20 days	Microscopic R.B.C. day 3 after biopsy
505	14	5	10	No bleeding in 29 days	
480	5	1	14	No bleeding in 24 days	

\*LMP, Last menstrual period.

In summarizing the points discussed, we may accept the following as valid: (1) The anterior hypophysis or any other single endocrine gland is not directly or actively responsible for the initiation of the menstrual flow. Such reaction follows inactivity or cessation of the ovarian hormones. (2) Withdrawal of either estrogen, progesterone after estrogen, or testosterone results in uterine bleeding. (3) Either testosterone or progesterone will prevent the bleeding of estrogen withdrawal. "Proges-

Testosterone propionate (perandren, Ciba) will prevent the bleeding of estrogen withdrawal in monkeys as effectively as progesterone.<sup>11</sup> After the usual ten-day treatment with an estrogen, 5 mg. of testosterone propionate will prevent the bleeding of estrogen withdrawal. Upon cessation of the testosterone, a latent period typical of estrogen withdrawal occurs (eight to ten days). However, after a progestational endometrium is established, dosages of 5 mg. and 10 mg. do not prevent bleeding nor change the time of the latent interval. Dosages of 25 mg. per day do effectively inhibit the bleeding (Fig. 4).

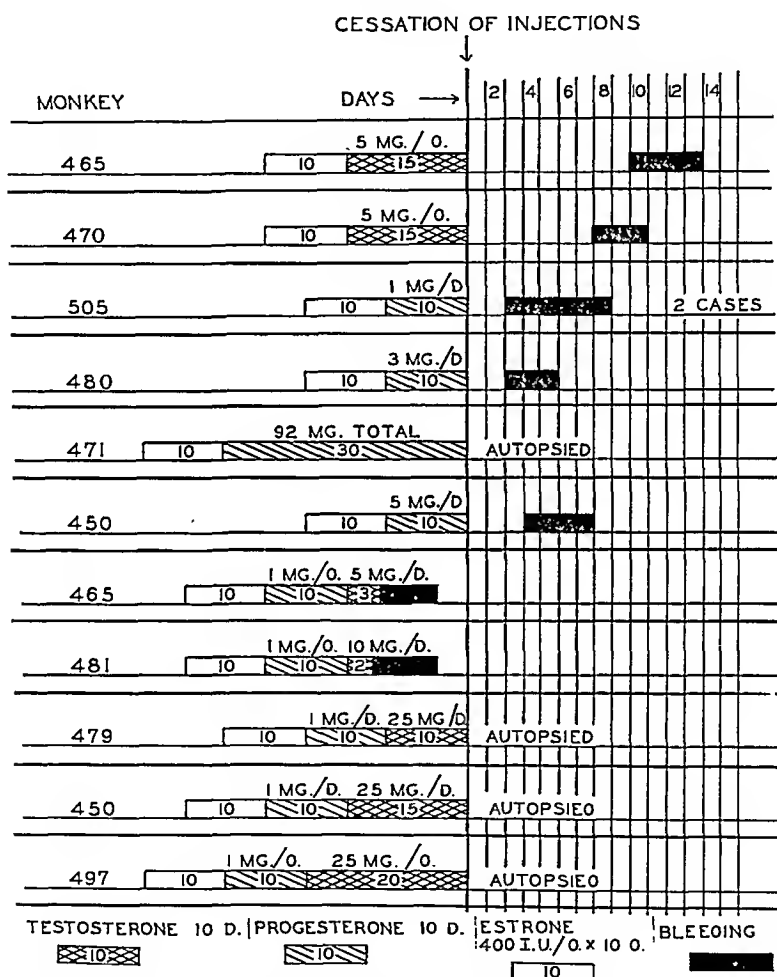


Fig. 4.—Graph showing the latent period for bleeding after testosterone treatment, and its inhibition by progesterone.

The endometrium of ovariectomized monkeys after testosterone injections which follow estrogen is clearly proliferative. That is, if an endometrium is prepared by estrogen, the subsequent treatment with testosterone maintains the histologic character of the proliferative (estrinized) endometrium. When estrogen is followed by progesterone and a secretory endometrium is formed, then adequate dosages of testosterone propionate continue to maintain the high secretory condition developed by



The case is certainly more clear because more limited and immediate in the case of progesterone withdrawal. In this instance, both in woman and the monkey, bleeding begins within forty-eight hours after progesterone withdrawal. If, during the pro gravid phase, progesterone merely prevents the protective function of the estrogen, as Corner suggests, it also circumscribes the action to a period of twenty-four hours.

It appears more reasonable to assume that the withdrawal of either hormone permits conditions to develop within the vascular supply or the tissue of the endometrium which leads to the phenomena of menstrual bleeding. In the case of progesterone, these changes become effective at once; after estrogen withdrawal the effect is not so localized in time, and it slowly becomes effective over a period of many days.

The estrogens (progynon B) and the progesterone (proluton) used in these experiments were generously supplied by Dr. Erwin Schwenk of the Schering Corporation. The testosterone propionate (perandren) was kindly made available by the Ciba Pharmaceutical Corporation, through the courtesy of Mr. Robert Mautner.

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Brunner, Endre K.: Criteria for Fertile Semen, J. Contraception 4: 77, 1939.

A specimen of fresh semen must be judged by the following four criteria: (1) volume of semen; (2) grade of sperm motility; (3) number of spermatozoa; and (4) percentage of abnormal sperms present.

A *good* specimen is more than 3 c.c. in volume; has 50 per cent or better motility six hours after ejaculation; has 50 millions or more sperm cells per c.c. and a minimum of 300 millions per ejaculate, of which 85 per cent must be oval in form, and not more than 7 per cent tapering.

A *fair* specimen is more than 2 c.c. in volume, has 35 per cent motile cells after six hours. The cell count is more than 20 millions per c.c. and a minimum of 150 million per ejaculate, of which more than 70 per cent are oval and not more than 15 per cent tapering.

Anything below these limits is classified as *poor*.

Judging from some of the exceedingly low values which were capable of procreation, it is impossible to condemn any specimen on a single examination. It seems, however, a fair assumption that for every criterion denoted as "poor" there must be at least one in the "good" column for the semen to be considered fertile.

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tin acts to prevent estrin from protecting the endometrium against bleeding."<sup>10</sup> (4) The length of the latent period between the withdrawal of estrogen and the withdrawal of progesterone is significantly and constantly different.

The endocrine balance in the normal menstrual cycle seems to be quite well established. The action of estrogens alone during the proliferative phase, and the development of the pro gravid or secretory phase through the combined action of estrogen and progesterone appear to be valid. The term "pro gravid" has been used to designate the histologic stage of endometrial development from the time shortly after ovulation to the cessation of active production of progesterone by the corpus luteum. All indications are that the last phase is a period of forty-eight hours or less which is the true premenstrual stage. It is at this stage of the cycle that attention must be focused to discover the factors which cause the hemorrhage and tissue fragmentation characteristic of menstruation (Fig. 5).

Coneomitant with the disappearance of progesterone, either in the artificial experimental cycle or in the normal cycle, several other phenomena have been clearly described by Bartelmez.<sup>16</sup>

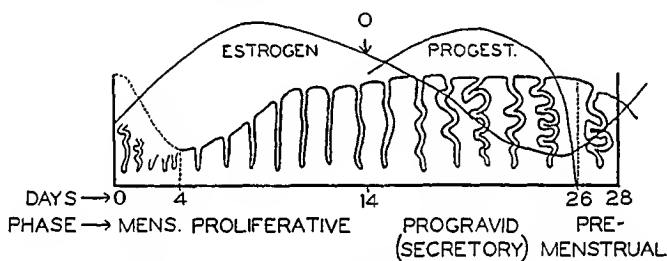


Fig. 5.—Graph of the stages of the endometrial cycle, indicating a possible hormonal balance effecting endometrial change and menstruation of hormone withdrawal.

The coiled endometrial arteries constrict at the base and the stroma of the endometrium becomes dehydrated. The process of dehydration is not understood but the tissue shrinks markedly. The arteriolar flow is supposed to be scanty, the pressure reduced. A peripheral ischemia ensues. This ischemia is the terminal result of the alternating "blush and blanch" arteriolar phenomena which Markee has observed in the ocular endometrial grafts. According to Markee (quoted by Bartelmez), the terminal ischemia lasts for from four to twenty-four hours. After this, subepithelial hematomas appear, followed by their coalescence into lacunae, which begin to bleed into the lumen. Very little tissue is lost during the first twelve hours of the hemorrhage.

It is obvious that the initiation of menstruation is caused or permitted by the withdrawal of one or more of the hormones discussed. The hormone withdrawal theories must assume that during the interval between withdrawal of the hormone and the actual hemorrhage something happens in the tissue of the endometrium. One of the effects of this something is the constriction of the base of the endometrial coiled arteries, with the resultant ischemia. Another coneomitant effect is the apparent dehydration of the stroma. The actual bleeding appears to be a result of these conditions.

were given over a period of fourteen days, at three-day intervals. This series was immediately followed by the injection of 50 International Units of proluton (synthetic progestin) in divided doses, within a period of seventeen days. In addition, two injections of 1,000 rat units of progynon B\* were given. Previous to medication the uterus measured two inches. Biopsy revealed an endometrium of a late follicular phase, no evidence of any luteal change (Fig. 3). Staining occurred for a period of six days. The uterus at the time of biopsy measured 2 1/8 inches. No staining thereafter. Hot flushes lasting a few seconds occur on rare occasions. Breast symptoms were present throughout.

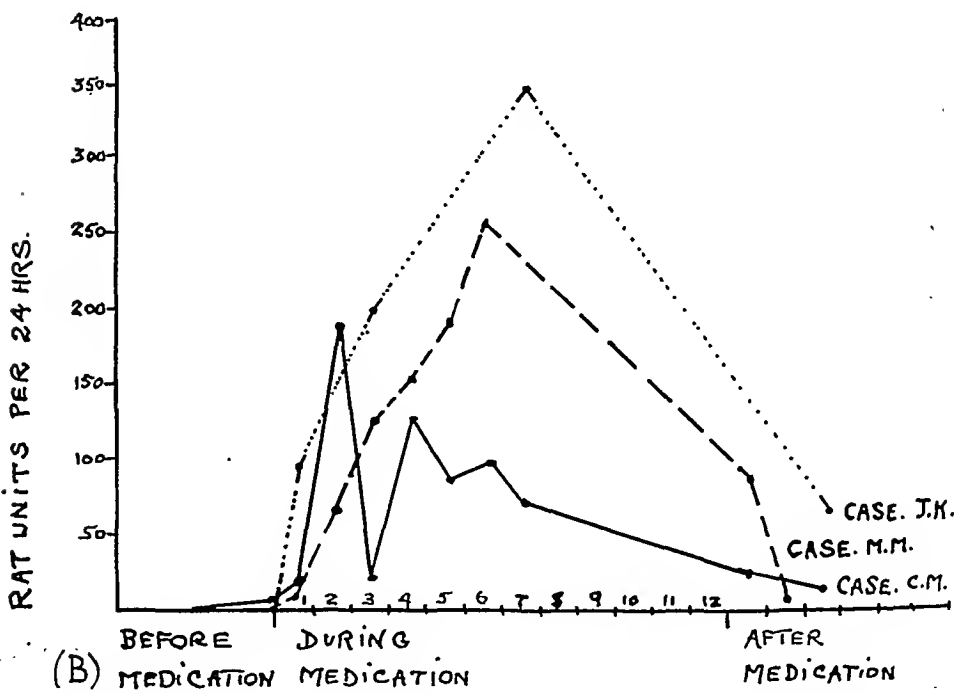
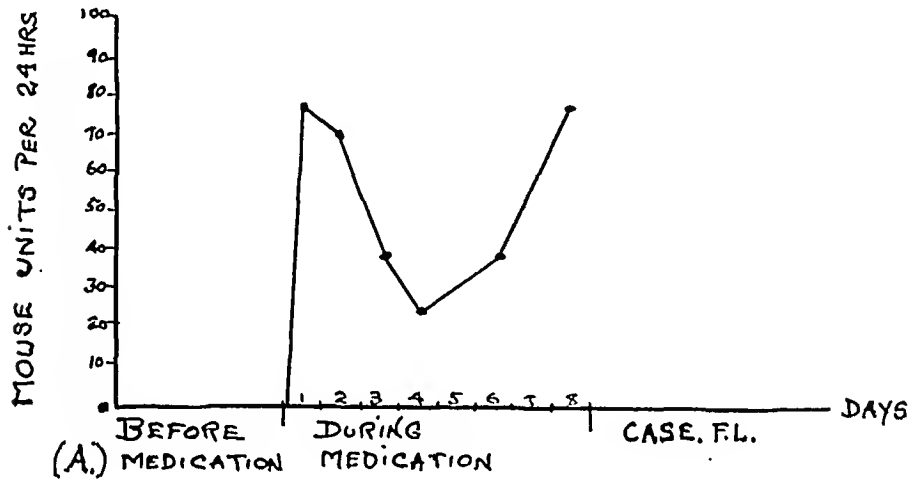


Fig. 1.—Assay of daily excretion of estrogenic hormone. A, Original chloroform method of Frank. B, Modification of chloroform method of Frank.

\*The injections of 1000 rat units were administered in error.

# THE EFFECT OF INGESTED ESTRONE (PROGYNON DH) AND PARENTERALLY ADMINISTERED SYNTHETIC PROGESTIN (PROLUTON) UPON THE HUMAN CASTRATE UTERUS

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IN A previous communication,<sup>1</sup> it was demonstrated that an ingested extract of estrin was capable of activating the atrophic endometrium of a human castrate. Since then several additional estrogenic substances have been isolated, and also synthetically prepared.

The present communication concerns itself with the action of dihydroxyestrin (progynon DH), a synthetic estrogenic substance with the formula  $C_{19}H_{24}O_2$ , on the atrophic endometrium of six human castrates. It also refers to the estrin-progestin (proluton) effect, and the urinary excretion of dihydroxyestrin as a supplementary index of biologic potency.

## CASE REPORTS AND EXPERIMENTAL PROCEDURES

CASE 1.—F. L.,\* white, female, married, aged 33 years, bilateral salpingo-oophorectomy for cystic ovaries. Menstruation began at 14, was irregular with occasional intervals of from three to six months, always painful and profuse, at times lasting thirty days. There had been 4 full-term pregnancies. The castration syndrome developed six months postoperatively.

A twenty-four-hour urinary specimen assayed for estrogenic activity was negative. One progynon DH tablet containing 1,000 active biologic units† was ingested daily for seven days and complete twenty-four-hour urinary specimens were collected and assayed by the chloroform method of Frank<sup>2</sup> (Fig. 1). Following a fifty-five-day interval, the same medication was repeated three times daily for a period of twenty-eight days. On the twenty-ninth day the endometrial biopsy showed an early follicular phase with congestion (Fig. 2).

After a thirty-day interval, the experiment was repeated with the exception that the same daily intake, 3,000 active biologic units, was continued over a period of sixty days, using approximately twice the total amount given previously. On the sixty-first day scanty tissue was recovered following curettage. Definite diagnosis was impossible although an occasional enlarged tortuous endometrial gland was present.

During the first part of the experiment, the patient described occasional spotty bleeding and during the latter course of medication there was staining for a period of twenty-eight days. There was more definite bleeding resembling menstruation during the last four days.

Following a two-year interval, another experiment was undertaken by using intramuscular injections of 50,000 rat units of progynon B. Five divided doses

\*This castrate was reported upon in a previous communication.

†An active biologic unit is the amount which, when taken orally, will produce approximately the same effect as one rat unit of the injectable preparation administered intramuscularly.

4). A complete twenty-four-hour urinary specimen assayed for estrogenic content, employing a modification<sup>3</sup> of the chloroform technique, was found to contain 4.8 rat units.

For a period of seven days the patient took one tablet (600 active biological units) of progynon DH daily. Complete twenty-four-hour specimens of urine were collected for nine days consecutively, and two additional specimens later on. The last two specimens were collected on the third and fifth days, respectively, after the ingestion of the last tablet. The results appear in Fig. 1.



Fig. 4.—Endometrium two months after castration. The glands show beginning atrophy and pycnotic changes. Atrophic endometrium of an early follicular phase.

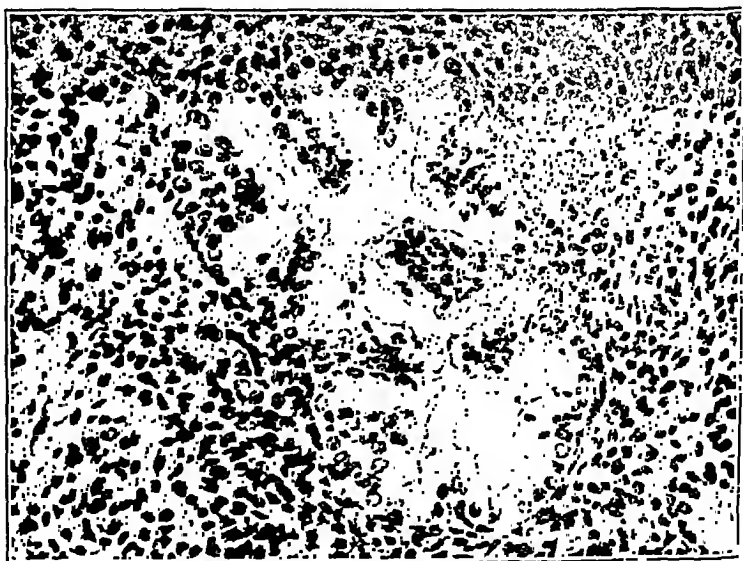


Fig. 5.—Definite luteal change following administration of 144,000 ABU of estrin and 60 International Units of progestin.

One month later for a period of fifteen days, the patient ingested 2,400 units daily of progynon DH. Bleeding occurred for three days during latter part of medication and the patient had the impression that she was menstruating again. Endometrial biopsy showed a normal, mid to late follicular phase. The uterine measurement was  $2\frac{1}{4}$  inches.

CASE 2.—C. M., aged 36 years, single, admitted to the Gynecological-Endocrine Clinic complaining of hot flushes every half hour. Previous history irrelevant, except for previous operations: Right ovary removed for cystic degeneration nine years previous and the left ovary removed for the same condition six weeks ago. Menstruation began at the age of 20 years, normal flow with five weeks' intervals which later changed to three weeks.

Bimanual examination revealed a small uterus, anterior in position and freely movable. The adnexa were not palpable. The cervix was small, atrophic and pale. The vaginal mucosa was pale and dry. The uterus measured two inches. Endometrial biopsy showed an atrophic endometrium in the early follicular phase (Fig.

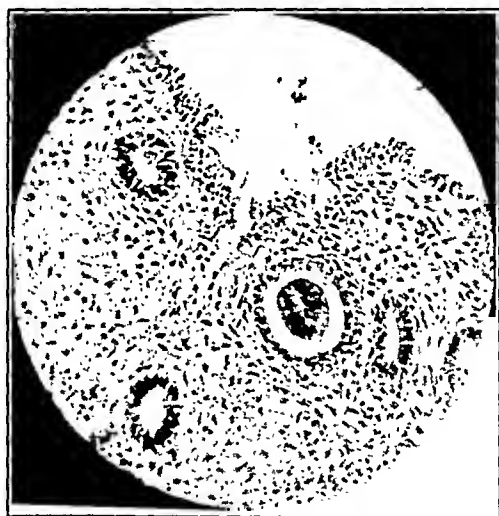


Fig. 2.—Endometrium taken after estrin therapy. The glands are slightly larger than those of an immediate postmenstrual type. Stroma is rather loose and very hemorrhagic. Early follicular phase.

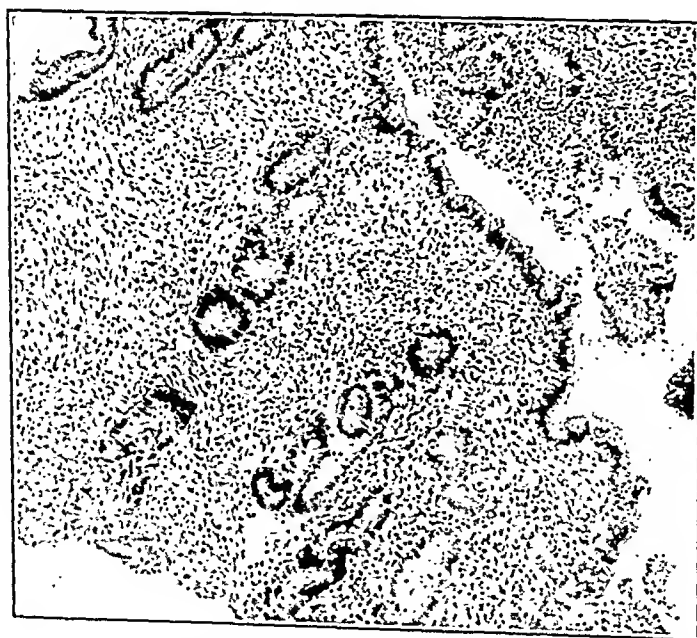


Fig. 3.—Late follicular endometrium with round cell infiltration of the stroma. No luteal change. (After method of Kaufmann.)

progynon DH tablets (600 units). Flushes disappeared after the third day of medication. For a succeeding period of twelve days, the patient ingested 7,200 units daily in addition to daily injections of 5 International Units of proluton, a total of 60 International Units. Slight staining began a day before cessation of medication. Biopsy revealed endometrium of a luteal phase (Fig. 6). The patient described manifestations of impending menstruation during the last three days of medication in addition to breast fullness and nipple sensitivity during the last ten days of medication. There were no hot flushes after the third day of medication. The vaginal mucosa was pinkish and moist, the cervix assumed its normal softness; the uterus measured  $2\frac{1}{2}$  inches. Three days following termination of therapy there was definite bleeding for four days.

CASE 4.—J. G., white, female, aged 24 years, single, complained of severe hot flushes occurring every ten to fifteen minutes, lasting two to three minutes with attacks of profuse perspiration, followed by cold, clammy sweats.

Following two induced abortions, the second of which terminated in pelvic inflammatory disease, an appendectomy and removal of the right tube and ovary were done, and a second operation was necessary for removal of the left tube and ovary seven months later. Bimanual examination revealed a small retroverted uterus, deviated to the left, measuring  $2\frac{1}{2}$  inches. The introitus admitted two fingers with difficulty, the vaginal mucosa was pale and dry, cervix slightly atrophic.

Menstruation began at  $13 \times 3 \times 28$ . There had been no menstruation for two months. Endometrial biopsy produced a scant amount of tissue which on microscopic examination revealed atrophic endometrium of an early follicular phase.

For a period of twelve days the patient ingested 4,800 units of progynon DH tablets daily. For a succeeding interval of twelve days, 7,200 units were ingested daily in addition to the injection of 5 International Units of proluton, a total of 55 International Units. Biopsy following the medication revealed endometrium of a follicular phase. The uterus measured  $3\frac{1}{4}$  inches. The vaginal mucosa was moist, of a normal pinkish hue, the cervix was soft and of normal color, and there was slight sanguineous oozing from the external os.

The flushes and attacks of perspiration gradually disappeared until the day of the second biopsy when the patient experienced only one flush per day. A sanguineous discharge appeared during medication and three days of bleeding began on the twenty-first day of medication. Four days after cessation of organotherapy the patient experienced six flushes per day. Twelve days after cessation of organotherapy the patient reported the occurrence of only a few flushes a day.

CASE 5.—P. Z., aged 40 years, widow, was admitted to the Gynecological-Endocrine Clinic complaining of hot flushes every one-half to two hours, followed by attacks of excessive perspiration, joint pain over entire body, headache, and dizzy spells. Last menstrual period occurred eight months previously when a bilateral salpingo-oophorectomy for cystic ovaries was performed. Bimanual examination revealed a small atrophic retrodisplaced uterus measuring  $2\frac{1}{2}$  inches. Vaginal mucosa dry and pale. Cervix very atrophic and dilatable under extreme difficulty. Endometrial biopsy revealed atrophic remnants of an early follicular phase.

Eight tablets daily of ethynyl estradiol (1.2 mg.) were taken for twelve days. No recurrence of symptoms during the entire time of medication. Hot flushes and dizziness disappeared. Endometrial biopsy on the thirteenth day showed a good late follicular phase. The vaginal mucosa was moist and of a normal pinkish hue. Cervix easily dilatable. After a two weeks' interval, 12 progynon DH tablets (600 ABU) were taken daily for twelve days followed by eight progynon DH tablets daily for twelve days plus one ampoule of proluton (5 International Units) daily. Slight staining occurred during medication. Endometrial biopsy showed an early luteal phase with cystic degeneration. Nuclei of the glandular epithelium were centrally placed with a clear basal zone present. In some areas there was beginning tufting. Four days of bleeding occurred six days after cessation of medication. At this time the patient was completely free of symptoms. One month later the flushes recurred. At this time the same medication was repeated for twenty-four days.

*Second Experiment.*—For a period of thirty days, 2,400 units were ingested daily, and for a following period of ten days, 2 International Units of proluton were injected daily, a total dosage of 20 units. The specimen obtained by biopsy was fixed in absolute alcohol and stained for glycogen with Best's carmine, but there was no evidence of glycogen in any part of the material. Bleeding occurred three days after the biopsy was taken and continued for eight days. During the entire duration of treatment, the patient was completely free from flushes. Seventeen days later the flushes recurred but were not as frequent or severe as prior to medication.

*Third Experiment.*—For a period of twelve days the patient ingested two tablets (600 units) three times daily and six tablets upon retiring, a total of 86,400 active biologic units. For a succeeding period of twelve days, the patient received one ampoule daily of 5 units of proluton, a total of 60 International Units, plus the continuation of two progynon DH tablets four times daily, an additional amount of 57,600 units. Spotting began the day preceding cessation of medication and bleeding appeared two days later. Endometrial biopsy showed areas of a late follicular phase, while other areas showed definite changes diagnostic of a luteal phase (Fig. 5). The uterine measurement at this time was  $2\frac{1}{2}$  inches. The cervix was soft, the vaginal mucosa was of a normal pinkish hue and moist.



Fig. 6.—Endometrium showing definite luteal change following administration of 144,000 ABU of estrin and 60 International Units of progestin.

CASE 3.—J. K., white, female, married, aged 22 years, was admitted to the Gynecological-Endocrine Clinic complaining of hot flushes and amenorrhea. Both ovaries were removed at two previous operations. Uterus left in situ with a Crossen suspension. Menstrual history  $15 \times 3 \times 30$ . For two years previous to operation she menstruated every two weeks for ten or eleven days, with a profuse painful flow. Last period four months previous. Flushes with headaches began soon after operation. Bimanual examination revealed a small uterus which was in anterior position, not freely movable. Adnexa not palpable. Uterine measurement was  $2\frac{1}{2}$  inches.

Two successive complete twenty-four-hour urine specimens (1,770 and 1,730 c.c.) were assayed for estrin and none found. For seven days one tablet of progynon DH (600 units) was taken daily. Complete twenty-four-hour specimens were submitted on the second, fourth, and seventh days and two specimens were submitted one and three days, respectively, after the ingestion of the last tablet. (Results are noted in Fig. 1.)

After a protracted interval scanty tissue was obtained by biopsy. Microscopic examination revealed atrophic remnants of an early follicular phase. For a period of twelve days, the patient ingested eight tablets daily, a total of 4,800 units of the



mann,<sup>11, 12</sup> Clauberg,<sup>13</sup> Elden,<sup>14</sup> Werner and others,<sup>15-17</sup> and myself.<sup>1</sup> Working independently of each other, the first two investigators succeeded in producing a luteal phase of endometrium in the human castrate by the daily injections of 10,000 mouse units of progynon benzoate for twenty-one days followed by 5 rabbit units of progestin (proluton) daily for seven days. Peculiarly enough, Elden and myself have been unable to corroborate these results, using 10,000 rat units of progynon B for five doses, followed by a total of 50 rabbit units of proluton, given in divided doses. Bleeding occurred within forty-eight hours after the last injection, as it did in the cases reported by Kaufmann and Clauberg. Case 1 (Fig. 3) is illustrative of this finding; the endometrial biopsy demonstrating a late follicular phase but no evidence of any luteal changes. Elden feels that several factors are involved, i.e., excess estrin, deficient progestin, or lack of balance between the two hormones. In three patients with long standing amenorrhea John Rock<sup>18</sup> reports that a total of 40 rabbit units of proluton caused demonstrable progestational changes in endometrium previously made to proliferate with huge doses of progynon B (50,000 rat units). These patients, however, possessed intact ovaries. The fact that estrone is secreted throughout the cycle should be emphasized, because my personal experiments in 6 human castrates were based on this knowledge. In a paper published in 1935 Kaufmann<sup>19</sup> alters his original therapeutic plan by increasing the dosage of estrin, i.e., 250,000 International Units of estrin for five doses every fourth day followed by five daily doses of 7 rabbit units of proluton. The total dosage of 1,250,000 International Units is equivalent to approximately 250,000 rat units, five times the original amount used. A late luteal phase was produced and the subject of Kaufmann's experiment began to bleed forty-eight hours later.

The present communication contains a departure from previous experimental procedures, not only as to the timing of medication but also utilizing the oral ingestion of estrin. Complete twenty-four-hour urinary specimens prior to treatment revealed the complete absence of estrogenic substances with the exception of Case C. M. (Fig. 1). Daily bio-assays following ingestion showed the presence of fairly large amounts of estrogenic substance, proving conclusively the biologic potency of the hormone used. In addition, urinary specimens received several days after final ingestion continued to show evidence of the hormone, indicating its cumulative action (Fig. 1).

In Case 1, 84,000 Active Biologic Units of dihydroxyestrin orally produced an active follicular endometrium, while in Case 2, 36,000 units for a period of fifteen days produced a mid to late follicular phase of endometrium. Again, in Case 2, after the administration of 72,000 Active Biologic Units of dihydroxyestrin followed by 20 International Units of proluton in divided doses, the biopsy specimens did not show the presence of glycogen nor a luteal phase of endometrium. The failure in this instance was undoubtedly due to the small dosage of progestin. Two months later the ingestion of 144,000 Active Bio-

The biopsy revealed several areas of endometrium which definitely showed changes ranging from early luteal to late luteal phase. At this time the patient was again completely symptom-free.

CASE 6.—C. L., white, married, aged 28 years, was admitted to Gynecological-Endocrine Clinic complaining of hot flushes and nervousness, excessive perspiration, especially during the night, and frequent frontal headaches. Bilateral salpingo-oophorectomy four years previously for bilateral dermoid cysts. Menstrual history 13 x 4 with irregular intervals. Two normal pregnancies and one spontaneous miscarriage. No menstruation since operation.

Bimanual examination revealed the uterus to be slightly smaller than normal, anterior position, freely movable, cervix small, well epithelized, uterus measured 2¼ inches. Endometrial biopsy revealed atrophic endometrium.

For a period of twelve days, the patient received eight progynon DH tablets daily (600 ABU). For a succeeding twelve days, 12 tablets daily were ingested in addition to the injection of 90 mg. of proluton in divided doses. Endometrial biopsy taken one day following the last injection revealed endometrium of a late luteal phase, uterus measured 3½ inches. At this time the hot flushes, attacks of perspiration, and headaches completely disappeared.

#### COMMENT

The majority of investigators agree that the normal corpus luteum secretes larger amounts of estrin than that of its predecessor, the mature Graafian follicle. This is obvious from the results obtained in blood examinations<sup>4-6</sup> of normal, fertile, menstruating women at various periods of the menstrual cycle, as well as consecutive urine examinations for estrin content. These findings are at variance with the opinion of Fluhmann,<sup>7</sup> who, on the basis of the test devised by him, reports the highest peak of estrin secretion just previous to ovulation and that a secondary rise appears prior to the onset of menstruation. Of primary importance, however, is the established fact that estrin is secreted during the entire normal cycle with the exception of the desquamative period, and the aggregate amount during the luteal phase is greater than that of the follicular phase. Another accepted fact is that a fully "estrinized endometrium" is necessary for progesterone to produce the luteal phase.

Hisaw and Leonards<sup>8</sup> originally stated that progestin could not transform rabbit endometrium, after castration atrophy, into a progestational condition. After further experimentation, Hisaw<sup>9</sup> alone reports mild, though definite, progestin changes in a juvenile monkey thirty-eight days after castration, giving 4 rabbit units of progestin daily for ten days. In the same paper he also reports a pre-secretory luteal effect, one far more pronounced than in the previous experiment, in an adult castrated monkey following the daily injection of 40 rat units of estrin for twenty-two days, followed by the combination of 73 rat units of estrin plus 4 rabbit units of progestin daily, for a period of ten days. In a third paper, Hisaw and his co-workers<sup>10</sup> report the production of progestational endometrial modification in castrated monkeys and rabbits with large doses of progesterone, small doses having little or no effect.

Animal experimentation, although of importance, does not necessarily always apply to changes in the human economy and consequently experimental efforts should be directed toward human criteria whenever possible. Very little experimental work with the human castrate uterus has been reported, with the exception of that of Kauf-

nullified a possible progestin effect. In all cases bleeding occurred during administration or after cessation of medication. The hot flushes and other symptoms characteristic of the menopausal syndrome were completely relieved during the period of treatment, but recurred in all cases some time after cessation of medication.

I wish to express my grateful appreciation to Dr. Walter T. Dannreuther for his kind assistance and efforts in making this work possible.

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27 EAST 93RD STREET

## THE ANTERIOR PITUITARY-LIKE HORMONE IN LATE PREGNANCY TOXEMIA\*

### A SUMMARY OF RESULTS SINCE 1932

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THE presence of abnormally high levels of the anterior pituitary-like hormone† in the serum and urine of patients with late pregnancy toxemia and eclampsia was first reported in 1933.<sup>2</sup> This finding has since been confirmed.<sup>3-6</sup> Quantitative assays of the anterior pituitary-like hormone in the serum and urine of patients during normal and pathologic pregnancies are still being carried on in this laboratory and at the present writing (March, 1939) 560 serums and 390 urines from 173 pregnant women have been titered. Results concerning 127 of these pregnancies have been previously reported in

\*The Mrs. William Lowell Putnam investigation of the toxemias of pregnancy.

†Commonly referred to as A.P.L. *Synonyms*: P.U. (pregnancy urinary hormone), pregnancy prolan, antuitrin S, follutein, antophysin (now labelled korotron), "A.P.L.," etc., etc. Since this gonadotropic factor of human pregnancy has been shown to be a product of chorionic tissue,<sup>1</sup> the logical appellation for it would be "chorionic gonadotropic hormone."

Analyses of placental tissue and tests upon hypophysectomized rats by us<sup>8</sup> have demonstrated that the excessive gonad-stimulating power of the serum of patients with late pregnancy toxemia is due to a factor which does not differ qualitatively from that found in normal pregnancy. Anselmino and Hoffmann<sup>9</sup> have reached the same conclusion concerning the gonadotropic hormone of late pregnancy toxemia.

logic Units of progynon DH for twenty-four days in addition to 60 International Units of proluton for the last twelve days produced a luteal phase. The third and fifth cases received similar amounts of the respective hormones within the same time limit, with the exception that the amount of estrin was reversed, i.e., 4,800 units daily for twelve days, followed by 7,200 units daily for twelve days, and here again luteal phases were produced in both instances. In these 2 cases the endometrial changes were more pronounced than in Case 2. In Case 4 there was bleeding for three successive days during the course of progestin therapy. For a period of two days the patient failed to receive proluton injections because of her illness. This, however, does not seem to corroborate the estrin depriving theory, for she continued the estrin therapy without interruption for twenty-four days. A resumption of the progestin therapy failed to produce any luteal changes, therefore it may be assumed that complete desquamation occurred during the period of bleeding. Since an early follicular phase was found in the endometrial biopsy, the progestin was doubtless ineffective during the latter half of treatment. In Case 6 the additional amount of progestin injected produced a later luteal phase comparable to that found just before menstruation in normal individuals. In all but one instance (Case 4), the vasomotor disturbances were completely relieved soon after beginning organotherapy, and yet shortly after discontinuing medication a recurrence of symptoms occurred in two cases. The disappearance of the menopausal syndrome is due to the estrin-progestin inhibition of the pituitary, despite the fact that it is only temporary. In all six cases bleeding began within forty-eight to ninety-six hours after medication was discontinued, although occasional staining (sanguineous discharge) appeared during medication. Some patients described symptoms of impending menstruation toward the end of treatment. In all instances there was definite evidence of uterine development, as determined by differences in length when the uterine cavity was measured before and after treatment. The atrophic condition of the vaginal mucosa and cervix regained a normal pinkish hue and moisture. Breast fullness and nipple sensitivity were described in all cases.

It is only possible to theorize regarding the practical application of this experimental work at the present time. The same therapeutic methods are now being utilized in the treatment of primary and secondary amenorrheas, particularly in cases in which the pituitary-ovarian relationship is within normal limits.

#### SUMMARY

Of 6 castrated human females a luteal phase of endometrium was produced in three by the administration of 144,000 ABU of progynon DH orally and 55 to 60 rabbit units of proluton, and in a fourth with an additional 30 units of proluton. In one case, following the method of Kaufmann, a luteal endometrium could not be obtained. In another instance bleeding began with the administration of progestin which

TABLE I. SERUM ANTERIOR PITUITARY-LIKE HORMONE IN LATE PREGNANCY. SUMMARY OF TOTAL RESULTS. 1932 TO FEBRUARY, 1939, INCLUSIVE. 173 CASES

CLINICAL DIAGNOSIS AT TIME OF DELIVERY	PATIENTS WITH NORMAL ANTERIOR PITUITARY-LIKE HORMONE	PATIENTS WITH HIGH ANTERIOR PITUITARY-LIKE HORMONE
Normal pregnancy	64, 71.1 per cent	
Pre-eclampsia or eclampsia	10,* 11.1 per cent	75, 90.3 per cent
Nephritic toxemia	9,† 10 per cent	
Essential hypertension	2,† 2.2 per cent	
Premature delivery at 6 to 8 months	5, 5.6 per cent	8, 9.7 per cent
Totals	90	83

\*Two of these patients died of eclampsia (1 came to autopsy). Two others are known to have gone through a subsequent pregnancy with no toxemia.

†Symptoms began early in pregnancy.

classified as pre-eclamptic or eclamptic, 75 had high values for serum anterior pituitary-like hormone and 10 had normal levels. Thus there were no normal pregnancies among the 83 patients with high anterior pituitary-like hormone, 90 per cent having been diagnosed as having pre-eclampsia or eclampsia and the other 10 per cent having delivered prematurely.

Table II summarizes 82 of the above 173 patients who were followed from the fifth month by repeated serum analyses with the purpose of determining whether

TABLE II. SUMMARY OF RESULTS OF REPEATED ANALYSES FOR SERUM ANTERIOR PITUITARY-LIKE HORMONE DURING THE FIFTH, SIXTH, AND SEVENTH MONTHS OF PREGNANCY. 82 CASES

CLINICAL DIAGNOSIS AT TIME OF DELIVERY	PATIENTS WITH NORMAL ANTERIOR PITUITARY-LIKE HORMONE	PATIENTS WITH ABNORMAL RISE
Normal pregnancy	36, 72 per cent	
Pre-eclampsia	2, 4 per cent	25, 78 per cent
Nephritic toxemia	6,* 12 per cent	
Essential hypertension	1,* 2 per cent	
Premature delivery at 7 to 8 months	5, 10 per cent	7, 22 per cent
Totals	50	32

\*Symptoms began early in pregnancy.

or not late pregnancy toxemia could be predicted prior to its clinical manifestation on the basis of serum anterior pituitary-like hormone values. In none of the 7 patients diagnosed as having nephritic toxemia or essential hypertension were the values at any time above the limits of normal. Twelve women had premature deliveries, 5 with normal and 7 with high levels of serum anterior pituitary-like hormone. *Of the 27 women who developed pre-eclampsia after the seventh month, 25 had had an unmistakable rise in serum anterior pituitary-like hormone four to six weeks previously.* Two women, in whom repeated serum analyses failed to reveal any abnormality, later developed toxemia. Thus none of the 32 women whose serum values exceeded normal levels during the fifth, sixth, or seventh month experienced a continued uneventful gestation. Twenty-five developed pre-eclampsia\* and 7 delivered prematurely at about the time when toxic signs might have been expected to appear.

## CONCLUSIONS

1. Pre-eclamptic toxemia and eclampsia are usually (88 per cent in this series) characterized by the finding of excessive amounts of an-

\*It should be emphasized that, although the highest values for serum anterior pituitary-like hormone have been encountered in cases of eclampsia, the degree of excess of this factor does not consistently bear a direct relationship to the severity of symptoms and signs.

detail.<sup>2, 7-10</sup> The total data which have accumulated during the seven years since the inception of this investigation seem sufficient to warrant separate summary.

Although urines and placentas from a large number of the cases included in this report have been assayed for the anterior pituitary-like hormone, the results of serum analyses only will be summarized. In the main, the findings in urines and placentas have been confirmatory of the serum titers, but the method for extracting the anterior pituitary-like hormone from the serum (see below) is more reliable than are those for urine or placental tissue. Moreover, the quantitative determination of any urinary constituent depends upon the accurate collection of a twenty-four-hour specimen. This can be accomplished only under the most rigidly supervised conditions, whereas the collection of blood involves no such chance for error. We have, therefore, in recent years come to rely almost entirely upon serum values. Furthermore, in any attempt to predict late pregnancy toxemia one must necessarily assay serum, since the urinary values for the anterior pituitary-like hormone do not rise to abnormal levels until toxemia has become clinically manifest, whereas excessive amounts in the serum are demonstrable four to six weeks prior to the development of toxic signs.<sup>10</sup>

Our criteria for normal levels of the gonadotropic factor in pregnancy are based upon the analyses of 210 serums from 64 patients who were normally pregnant and continued so to delivery. In 36 of these cases, serum assays were performed at intervals from as early as the sixth week of gestation to delivery. The rest were studied by single specimens during the last trimester. A peak in the curve of the anterior pituitary-like hormone in both the serum and urine has been found to occur at about the time of the second missed period,<sup>10-13</sup> the values at this time being frequently as high as or higher than those observed in cases of chorionepithelioma or hydatidiform mole. This high level, however, is maintained for only a comparatively short time, one to three weeks, a fact which supplies an important means of differentiating between early pregnancy and mole. By the beginning of the fourth month the anterior pituitary-like hormone of serum and urine has reached a constant low level and in no instance of normal pregnancy between the fifth and eighth months have the serum values been higher than 100 R.U. per 100 c.c. During the last four weeks of gestation in a number of cases the serum anterior pituitary-like hormone rose somewhat above this amount. Values above 100 R.U. per 100 c.c. prior to the fifth missed period or within four weeks of term are therefore not considered abnormal.

In Table I the 173 cases studied in late pregnancy have been divided into those with normal and those with high levels of anterior pituitary-like hormone. None of the 11 with a clinical diagnosis of nephritic toxemia or essential hypertension had elevated serum anterior pituitary-like hormone—that these cases were probably diagnosed correctly is supported by the fact that signs were present by the second trimester. A total of 13 women had premature deliveries, 5 of these with normal and 8 with excessive amounts of anterior pituitary-like hormone. Of the 85 patients

with the precipitate, forming a smooth emulsion. The ether held back by the precipitate and saline is removed by stirring the contents up onto the sides of the centrifuge tubes while rotating, warming with the hand and blowing into the tubes. (No more heat than this should be applied—to avoid the possibility of any destruction of the hormone.) The stirring rods are washed down with 3 c.c. of saline, making the total content of each tube 6 c.c., this being the final test solution.

Each extract is administered subcutaneously into a nineteen- to twenty-one-day-old female rat, the injections being given twice a day for three days, 1 c.c. per injection. On the morning of the fifth day (ninety-six hours from the first injection) the rats are sacrificed and the ovaries examined for the appearance of *grossly visible discrete corpora lutea*. The anterior pituitary-like hormone of the serum being tested is considered normal provided none of the test animals or only the animal receiving the extract of 1.0 c.c. (test for 100 R.U. per 100 c.c.) gives a positive result. If all the animals show discrete corpora, the serum may be said to contain more than 333 R.U. of anterior pituitary-like hormone per 100 c.c., a definitely elevated level. If the animal receiving the extract of 1.0 c.c. and the 2 animals receiving the extract of 0.5 c.c. are positive, whereas the fourth animal has no corpora lutea, the serum may be said to contain 200 R.U. of anterior pituitary-like hormone per 100 c.c., an amount exceeding normal. For clinical purposes only 4 such tests are required with any 1 serum, unless the test for 333 R.U. per 100 c.c. is negative and the 2 tests for 200 R.U. per 100 c.c. fail to give check results. In this event the test for 200 R.U. per 100 c.c. is repeated on 2 more immature rats, and if more than 1 of the 4 animals receiving an extract of 0.5 c.c. show definite corpora, the anterior pituitary-like hormone may be considered to exceed normal levels.

Inasmuch as the reading of the end point requires considerable experience and even then is not always clear-cut, the importance of making check determinations with further specimens from the same patient and of using a series of at least 4 tests for each serum cannot be over-emphasized. No patient should be reported as having excessive anterior pituitary-like hormone unless high values are acquired in at least 2 specimens of serum.

#### DISCUSSION

It is logical to assume that the abnormal rise of serum anterior pituitary-like hormone, being the earliest indicator both of an hormonal imbalance and of impending pre-eclampsia or premature delivery, is most closely associated with the *primary* etiology. This, however, is not the only hormonal abnormality which has been found to characterize the disease. Quantitative determination of the estrogens has revealed that these are relatively low in the urine, serum, and placentas of toxemic patients.<sup>2, 7-10</sup> Urinary pregnandiol (the excretion product of progesterin) has also been found to be below normal levels.<sup>14, 15, 19</sup> A detailed study of urinary estrogens,<sup>14, 19</sup> in which 3 different estrogenic factors have been assayed separately, indicates that progesterin deficiency results in a marked change in the metabolism of the estrogens and in their more rapid destruction. Evidence for such a progesterin-deficient metabolism of the estrogens has been found thus far in 8 pre-eclamptic patients at the time of the development of toxic signs.<sup>17</sup> The hypothesis has been proposed that some change associated with a faulty metabolism of the estrogens due to progesterin deficiency (such as a toxic estrogen breakdown product) may be directly responsible for the generalized vascular derangement of pre-eclampsia and eclampsia.<sup>14</sup> Whether or not this hypothesis proves to be correct, our quantitative

terior pituitary-like hormone in the serum. This excess has been found to precede clinical signs by four to six weeks.

2. In a small percentage of cases with a clinical diagnosis of pre-eclampsia or eclampsia, the serum anterior pituitary-like hormone does not exceed normal levels.

3. In patients quite definitely diagnosed as nephritic or hypertensive (symptoms beginning earlier in pregnancy), the serum anterior pituitary-like hormone is normal.

4. Premature delivery may or may not be associated with excessive anterior pituitary-like hormone.

5. The finding of high levels of this substance in the serum during the fifth, sixth, or seventh month warrants the prediction of impending pre-eclampsia or premature delivery.

Quantification of serum anterior pituitary-like hormone during the fifth, sixth, and seventh months of pregnancy has become an accepted procedure both in this laboratory and at the New England Deaconess Hospital (Boston), where diabetic patients (in whom the incidence of premature delivery and pre-eclamptic toxemia is high) are being studied.\* It has been found of considerable value as a means of predicting later trouble and governing the management of patients. For this reason it seems advisable to include in this report an exact description of how these tests are performed.

At two- to three-week intervals between the fifth and eighth months of pregnancy, 10 c.c. of venous blood are collected without any anticoagulant and the clot allowed to form. The serum is separated, cleared of any cells by centrifugation and measured accurately into four 15 c.c. centrifuge tubes, each tube to contain 1.0 c.c., 0.5 c.c., 0.5 c.c., and 0.3 c.c., respectively. About 10 c.c. of 95 per cent ethyl alcohol is added to each tube, the contents mixed and the tubes placed in the refrigerator for twelve to 18 hours. After centrifuging and pouring off the supernatant alcohol, the precipitate is washed (stirring rod and shaking) once with ether, approximately 12 c.c., and again centrifuged. The ether is then poured off and the tubes allowed to drain for a few minutes, after which 3 c.c. of normal saline is added and mixed

\*Of the 173 patients followed, 31 were diabetic patients under the care of Drs. E. P. Joslin, Priscilla White, and R. S. Titus, of the George F. Baker Clinic of the New England Deaconess Hospital, Boston. In 25 of these, repeated analyses were performed. They are not considered separately, since the conclusions reached for the whole group apply equally well to diabetic pregnancies alone. There were 10 normal pregnancies, all with normal levels of anterior pituitary-like hormone in the serum. In the one case of nephritic toxemia, the values for serum anterior pituitary-like hormone never exceeded normal. Seven diabetic patients delivered prematurely, 3 with normal and 4 with high levels of serum anterior pituitary-like hormone. All 13 of the diabetic patients who had symptoms diagnosed as pre-eclampsia had excessive amounts of anterior pituitary-like hormone in the serum. Thus, there were no normal pregnancies among the 17 cases with high anterior pituitary-like hormone. Of the 15 patients in whom an abnormal rise was detected during the fifth, sixth, and seventh months, 11 developed pre-eclampsia some weeks after the first abnormal rise, and the other 4 delivered prematurely. As in nondiabetic patients, premature delivery may or may not be associated with high anterior pituitary-like hormone, but the incidence of premature delivery (rather than pre-eclampsia) in the high anterior pituitary-like hormone group was considerably greater among the diabetic patients (23.5 per cent) than among the nondiabetic patients (6 per cent).

In all of our studies of pregnant diabetic women we have received the indispensable cooperation of Dr. Priscilla White in the collection of specimens and supplying of clinical data. Of the 31 diabetic patients included in this series, 27 are being separately reported by her and others,<sup>18</sup> with especial reference to the clinical application of the quantification of serum anterior pituitary-like hormone in diabetic pregnancies.

†The serum is concentrated by alcohol precipitation for two reasons: first, to remove estrogens which when injected simultaneously enhance the anterior pituitary-like hormone reaction in immature rats, and, second, to reduce the toxicity. The method described gives quantitative recovery of anterior pituitary-like hormone added to serum.



placenta to be deficient in the utilization of anterior pituitary-like hormone for production of estrogen and progèstin. It is entirely conceivable that a failing utilization of anterior pituitary-like hormone might be accompanied by decreased formation in which event no abnormality would be revealed by its quantification. It is further conceivable that decreased formation might result from damage to the placenta by toxic separation, pre-eclampsia, or eclampsia. Such situations could explain the normal values for serum anterior pituitary-like hormone found in 12 per cent of the pre-eclamptic and eclamptic patients as reported above.

The fact that 22 per cent of the patients in whom an abnormal rise of serum anterior pituitary-like hormone was detected during the fifth, sixth, and seventh months delivered prematurely deserves comment. All the factors involved in the initiation of labor have not been ascertained but quantitative studies in women have revealed a marked drop in estrogens just before delivery,<sup>16, 17, 19</sup> and a decrease in progèstin has also been indicated by the changed metabolism of the estrogens which accompanies normal labor.<sup>17, 19</sup> The same hormonal changes which precede and accompany the onset of pre-eclampsia, therefore, appear to pertain rather suddenly at the time of normal delivery. Under certain conditions these changes might be associated with premature delivery rather than toxemia.

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The author believes that the practical value of repeated vaginal smears is not recognized sufficiently because of technical difficulties in staining them. He suggests fixing in equal parts of alcohol and ether, in which the slides can be kept indefinitely. Before staining, the slide is covered with methyl alcohol for two minutes, and then stained with diluted Giemsa prepared by adding 10 drops of the standard solution of 5 c.c. of distilled water. Staining requires twenty minutes. Cornified cells are stained red, partially cornified ones violet, and noncornified cells blue.

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studies of pre-eclampsia point toward the following sequence of events:

(1) Excessive amounts of circulating anterior pituitary-like hormone, (2) a decrease of progesterin and "total" estrogen at a time when they normally increase, and (3) a striking change in the metabolism of estrogens due to reduced progesterin, this last abnormality being demonstrable at the time of the onset of clinically recognizable toxemia. The role of anterior pituitary-like hormone, which distinguishes human pregnancy from that of practically all other mammals, in the physiology of normal gestation has not been ascertained, but one naturally supposes that this gonadotropic factor plays an important part in the placenta's elaboration of progesterin and estrogen, since it is such a potent stimulator of these factors from the ovaries of experimental animals. Of course the placenta has not been proved the source of progesterin and estrogen, but the circumstantial evidence pointing toward it as the source is overwhelming. There come to mind 3 possible explanations for the apparent paradox introduced by the finding of high levels of anterior pituitary-like hormone together with a deficiency of progesterin and estrogen in pre-eclampsia. (1) The increase of the gonadotropic substance may be a protective measure, an attempt to counteract a failing production of progesterin and estrogen. If this explanation were correct, one would expect the increase to follow rather than precede the drop in urinary estrogens and pregnandiol. (2) Excessive amounts of anterior pituitary-like hormone, due to an imbalance of placental function, over a sufficiently long period may have, in certain patients, an inhibitory influence upon the secretion of progesterin and estrogen, just as its prolonged administration experimentally is known to result in ovarian atrophy due to the stimulation of antibodies. If this were the case, the presence of antibodies in the material being assayed would inhibit the reaction and depress the titer. (3) To us, the most plausible explanation lies in a failing utilization of anterior pituitary-like hormone in the production of these steroids and consequent building up of the level of anterior pituitary-like hormone in the blood. This third hypothesis is supported by the following considerations. In normal pregnancy a rapid decline in the level of anterior pituitary-like hormone takes place during the third and fourth months. This decline coincides both with a rapidly increasing elaboration of estrogens and progesterin (based on urinary estrogen and pregnandiol) and with the "taking over," presumably by the placenta, of the functions of the regressing corpus luteum. These events are in accord with the idea that anterior pituitary-like hormone is utilized normally for the secretion of estrogen and progesterin by the placenta, and that, in being so utilized, its level in the circulation is kept low. Since the low level of serum anterior pituitary-like hormone is maintained during the fifth, sixth, and seventh months of normal gestation, during which time the production of estrogens and progesterin steadily increases, an abnormal rise would be interpreted as failure of utilization. On this basis one would place the primary etiology of pre-eclampsia in whatever causes the

Shapiro and Zwarenstein<sup>20</sup> have found that progesterone causes ovulation in the normal and hypophysectomized amphibian. McKeown and Zuckerman<sup>21</sup> have likewise found fresh corpora lutea and mature follicles in normal cyclic female rats which had received 1 mg. of progesterone daily for from nine to eleven days despite the suppression of the estrous cycles in 6 of the 7 animals. Selye, Browne and Collip,<sup>22</sup> on the other hand, have found that the daily administration of 4 mg. of progesterone for a period of twelve days in normal cyclic rats causes inhibition of follicular growth and atrophy of the ovaries.

The need for re-investigation of the effect of chemically pure progestin on the ovaries and related endocrine glands is evident from the foregoing summary of the problem. The experimental work herein reported was undertaken with this objective in view.

#### METHOD

Employing adult rats, three series of progesterone-injection experiments were executed as follows:

*Experiment I.*—Sixteen adult, female rats were each given subcutaneously 0.5 mg. of progesterone\* in 0.2 c.c. of sesame oil 3 times weekly for nine and one-half weeks (sixty-seven days). The total amount of progesterone administered to each rat during the course of sixty-seven days was 14.0 mg. Ten additional, adult, female rats, serving as controls, were each given subcutaneously 0.2 c.c. of sesame oil for an equal length of time.

*Experiment II.*—Six adult, female rats were each given subcutaneously 1.0 mg. of progesterone in 0.1 c.c. of sesame oil *daily* for thirty days. An additional group of 6 adult, female rats, serving as controls, were each given 0.1 c.c. of sesame oil *daily* for the duration of the experiment.

*Experiment III.*—Five adult, female rats were each given subcutaneously 4.0 mg. of progesterone in 0.4 c.c. of sesame oil *daily* for twelve days. The total amount of progesterone administered to each rat, during the course of twelve days, was 48 mg. Each of five additional animals, serving as controls, received 0.4 c.c. of sesame oil *daily*.

Daily vaginal smears were made and the estrous cycles recorded. All animals in each series were killed on the day following the last injection of progesterone. The ovaries, pituitary gland, and adrenals were extirpated, weighed and examined microscopically (Table I, Figs. 1 to 4).

#### RESULTS

*Effect on the Ovaries.*—The weight and morphology of the ovaries were unchanged by the sixty-seven-day course of treatment with 0.5 mg. of progesterone thrice weekly. Growing follicles, in all stages of development, and multiple fresh corpora lutea were present in the ovaries of both the treated and control groups of animals (Figs. 1 and 2).

The average weight of the ovaries in the two groups of rats which received the larger quantities of progesterone over a shorter period of time was somewhat lower than that of the respective control groups. This was especially apparent in the 4 mg. series (Table I). The microscopic appearance of the ovaries betrayed the deleterious effects of what may be assumed to be excessive doses. There were fewer growing follicles and no fresh corpora lutea. However, even the largest quantity of progesterone (4 mg. daily for twelve days) failed to suppress ovarian function entirely (Figs. 3 and 4).

\*Proluton, a synthetic progesterone, was employed through the courtesy of Drs. Gregory Stragnell and Erwin Schwenk of the Schering Corporation, Bloomfield, N. J. Assayed in our laboratory, 1 mg. of proluton was found to equal a Corner rabbit unit.

# THE EFFECT OF CRYSTALLINE CORPUS LUTEUM HORMONE, PROGESTERONE, ON THE OVARIES AND RELATED ENDOCRINE ORGANS

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THE recent availability of chemically pure corpus luteum hormone and its increasing employment as a therapeutic agent emphasize the importance of re-examining the accumulated experimental data (derived from the use of the crude product) on the effect of the hormone on the ovaries and related endocrine glands. Following Beard's<sup>1</sup> suggestion that the presence of the corpus luteum prevents ovulation during pregnancy, many corpus luteum extirpation experiments supported the thesis that the corpus luteum hormone suppresses follicular activity and inhibits ovulation.<sup>2-4</sup> It was shown later that the administration of impure progestin-containing extracts temporarily suppresses both growth of ovarian follicles (with loss of estrous cycles) and ovulation in rats,<sup>5,6</sup> guinea pigs<sup>7-11</sup> and in rabbits.<sup>12-14</sup> While such laboratory data should not be too eagerly translated into clinical equations, their importance to gynecology cannot be lightly estimated. If, as indicated in the earlier experiments, the corpus luteum hormone really inhibits follicular growth and ovulation, it must be administered with circumspection to women of childbearing age, although in some instances hormonal sterilization as attempted by Haberlandt<sup>15</sup> may be desirable.

It is certainly conceivable that some of the biologic effects previously attributed to progestin may have been caused by the presence of contaminants, such as injurious chemicals or small quantities of estrogen, in the progestin-containing extracts. The degeneration of the liver as well as of the ovaries, observed by Kennedy<sup>12</sup> in rabbits treated with an impure extract of corpora lutea, is mute testimony to the presence of unknown toxic agents in the product he employed. The admixture of estrogen in the early preparations of progestin was responsible for certain effects formerly believed to be specific for the corpus luteum hormone. For instance, both relaxation of the pubic joint<sup>16</sup> and vaginal mucification<sup>17</sup> have been recently elicited by administration of subminimal doses of estrogen alone.<sup>14, 18</sup> These changing concepts concerning the true physiology of the corpus luteum hormone make re-investigation with progesterone imperative. This has already been accomplished in reference to the uterine effects of progesterone. The pure product does inhibit uterine motility and converts the estrogen-primed endometrium into a pregravid state.<sup>19</sup>

Investigation of the effects of progesterone on the ovaries was, to the best of our knowledge, thus far attempted by three groups of investigators, with discordant results.

no significant difference (Table I). We are, nevertheless, not unmindful of the fact that functional inhibition may be present without change in weight of the organ. Considered, however, in the light of the undisturbed estrous cycles and the unchanged ovarian morphology in the 0.5 mg. series, the absence of pituitary weight changes suggests that physiologic quantities of progesterone cause no alteration in pituitary function of the rat.

*Effect on the Adrenals.*—The average weight of the adrenals of the three series of progesterone-treated rats did not differ from that of the control groups (Table

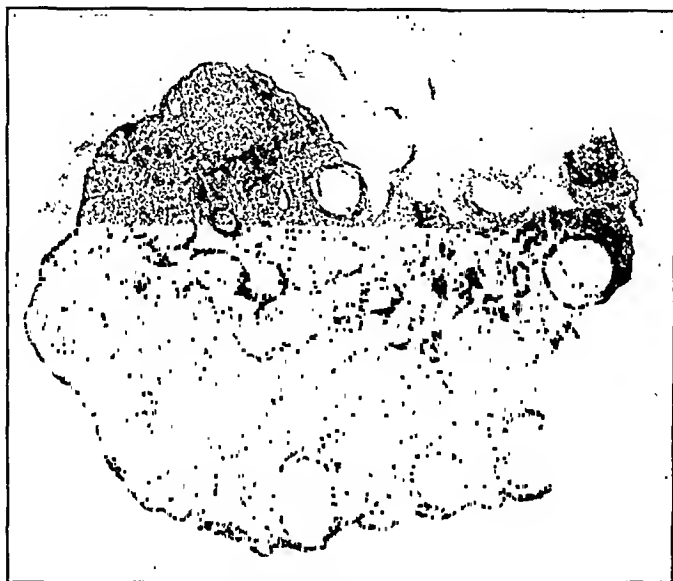


Fig. 3.—(Exper. II.) Photomicrograph of an ovary of an adult rat injected with 1.0 mg. of progesterone daily for thirty days, showing a decrease in size, degenerated follicles, and no fresh corpora lutea. ( $\times 24$ .)

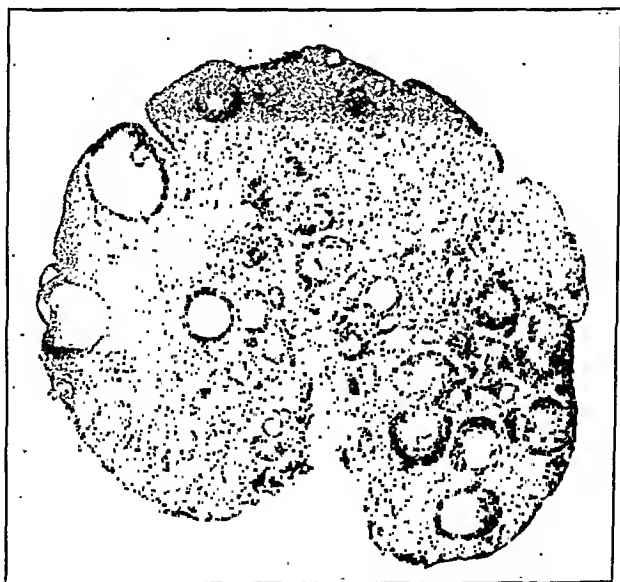


Fig. 4.—(Exper. III.) Photomicrograph of an ovary of an adult rat injected with 4.0 mg. of progesterone daily for twelve days, showing a decrease in size, many atretic follicles, and no corpora lutea. ( $\times 24$ .)

*Effect on the Pituitary Gland.*—Recognizing that the entire subject of pituitary cytology is presently undergoing rigorous re-investigation<sup>23</sup> and wishing to avoid any dubious interpretation of questionable histologic alterations attributable to progesterone treatment, we are eliminating a description of the microscopic appearance of the pituitaries. Reliance is placed solely on relative weight in which there was



Fig. 1.—(Control.) Photomicrograph of an ovary of an untreated adult rat, showing many mature follicles and a corpus luteum. ( $\times 24$ .)

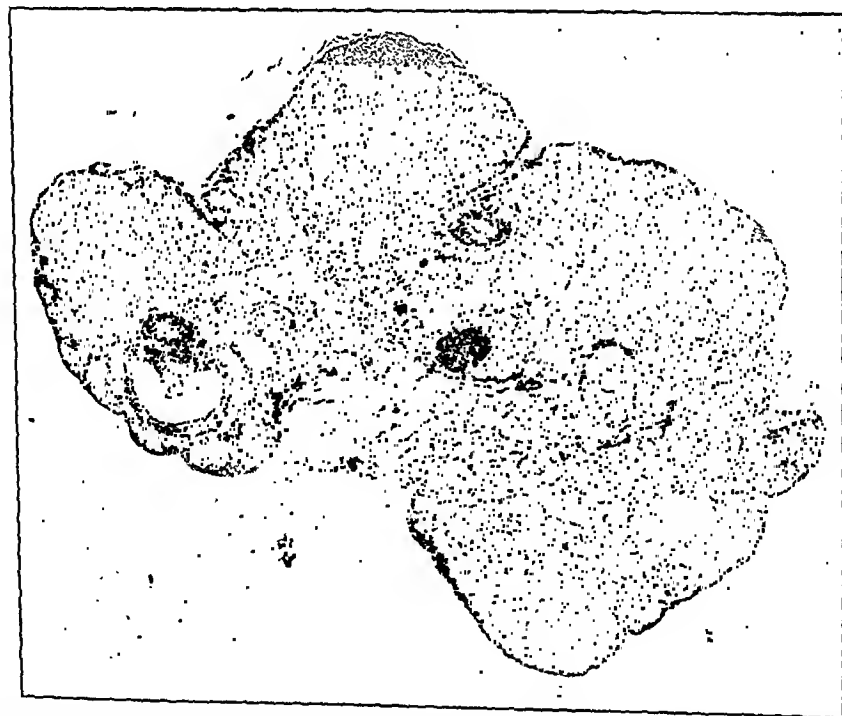


Fig. 2.—(Exper. I.) Photomicrograph of an ovary of an adult rat injected with 0.5 mg. of progesterone every other day for sixty-seven days, showing mature follicles and well-developed corpora lutea. ( $\times 24$ .)

The quantity of active hormone administered to each rat in the first experiment, namely, 0.5 mg. every other day for sixty-seven days, is far greater than that present in the *crude* extracts which produced follicular inhibition and is evidently more than sufficient for the species employed. In fact, the quantity received weekly (1.5 mg.) by each of the treated rats in Experiment I is more than sufficient to produce complete progestational changes in the endometrium of an estrogen-primed castrated rabbit weighing 3 kilograms. Moreover, the total dose (14 mg.) given each rat of this series is equal to the quantity of progesterone capable of suppressing the menstrual cycle of the adult monkey,<sup>19</sup> and is nearly half the quantity capable of evoking the secretory phase in the endometrium of an estrogen-primed human castrate.<sup>26-28</sup> Considered in the light of these data, it is fair to conclude that the absence of follicular inhibition in the first group of rats cannot be attributed to inadequate dosage.

The inhibition of follicular growth and the altered estrous cycles in the other two groups of rats attest to the harmful effect of unphysiologic quantities of progesterone. The larger the dose, the greater the follicular inhibition as seen in the group of rats given the largest quantity of progesterone, namely, 4 mg. daily for twelve days. This confirms the observations of Selye and his co-workers.<sup>22</sup> However, even a relatively large quantity such as 1.0 mg. daily for thirty days does not completely suppress follicular growth and uniformly inhibit estrus.

These experiments illustrate that it is the *total quantity* of progesterone and not the length of time of its administration which causes inhibition of follicular growth. Fourteen milligrams of progesterone administered over a period of sixty-seven days produced no deleterious effect, whereas double the quantity (30 mg.) spread over a period of only thirty days did produce considerable ovarian damage.

On the basis of these experiments and our clinical observations, we are justified in assuming that the clinical use of progesterone in doses of 5 to 20 mg. daily for a period of two weeks, and of smaller doses over a period of months, is safe.

#### SUMMARY

Unlike impure progestin products, progesterone, the crystalline corpus luteum hormone, administered in doses of 0.5 mg. thrice weekly for nine and one-half weeks to normal adult rats produced no inhibition of follicular growth, ovulation, and luteinization. The estrous cycles continued unabated. Nor was there any change in the average weight of the pituitary, adrenals, and ovaries. Evidence is adduced from the literature to emphasize that this quantity is more than enough for the physiologic needs of the rat.

Larger doses, such as 1 mg. daily for thirty days or 4 mg. daily for twelve days, produced definite inhibition of follicular growth and prevented ovulation and luteinization. These effects are apparently the result of excessive and obviously unphysiologic dosage.

TABLE I. EFFECT OF VARIED QUANTITIES OF PROGESTERONE ON THE AVERAGE WEIGHT OF THE OVARIES AND RELATED ENDOCRINE ORGANS OF ADULT FEMALE RATS

	EXPERIMENT I		EXPERIMENT II		EXPERIMENT III	
	TREATED	CONTROL	TREATED	CONTROL	TREATED	CONTROL
No. of rats	16	10	6	6	5	5
Dose of progesterone	0.5 mg. e.o. day for 67 days	0	1.0 mg. daily for 30 days	0	4.0 mg. daily for 12 days	0
Body weight (gm.)	175	160	171	175	159	164
Ovaries (mg.)	51	54	42	56	38	50
Pituitary (mg.)	10	10	10.5	9.4	7.8	9.6
Adrenals (mg.)	39	35	42	42	37	39

I). Likewise, no striking histologic changes were noted in the adrenals of the treated animals, the architecture of the cortical zones and the vascularity of the medulla appearing the same in all groups.

*Effect on Estrus.*—Regular estrous cycles continued unabated at intervals of from four to five days in all rats which received 0.5 mg. of progesterone every other day for sixty-seven days. The average number of estrous cycles per rat during the course of sixty-seven days was 14 in the treated and 16 in the controls. All but 2 of the 6 rats which received 1.0 mg. of progesterone daily for thirty days continued to have regular estrous cycles at intervals of from four to seven days during the thirty-day period, despite the known tendency of progestin to inhibit *vaginal* estrus. Three of the 5 rats given 4 mg. of progesterone daily for twelve days had one estrous cycle near the termination of treatment and the remaining 2 were anestrus.

The uninterrupted periodicity of the estrous cycles in the first group, despite the chronic administration of progesterone, was naturally a reflection of undisturbed ovarian activity. The partial or complete loss of estrous cycles in the two groups of rats given the larger quantities of progesterone indicates that the hormone does, when given in quantities far above the physiologic level, depress follicular growth and maturation. It is, however, significant that even a quantity as large as 4 mg. daily for twelve days does not uniformly suppress the estrous cycles.

#### DISCUSSION

It is evident from the above-described experiments that the prolonged administration of progesterone in physiologic quantities does not inhibit follicular growth, ovulation, and luteinization in the normal cyclic rat as do other active sterones, such as estrogen<sup>24</sup> and testosterone.<sup>25</sup> This observation is corroborated clinically, since we and others have found that the administration of 10 mg. of progesterone daily to women during the second half of the menstrual cycle—a total quantity more than sufficient to produce a progestational endometrium in the estrogen-primed uterus of the castrated woman—does not interfere with the menstrual rhythm, either immediately or remotely. When, however, huge doses, far in excess of physiologic needs, are experimentally administered, follicular growth, ovulation, and luteinization are inhibited.



and may be interpreted in general as an index of the level of blood cephalin. Normal values have been determined by Kirk, Page and Van Slyke<sup>5</sup> and by Andrus and Moore.<sup>6</sup> The latter investigators concluded that any value exceeding 2.00 mg. of alpha amino-nitrogen per 100 gm. of whole blood is definitely abnormal and indicative of liver damage.

A control group of 9 normal pregnant women was chosen and fasting blood samples were taken between the twenty-sixth and thirty-second week of pregnancy, between the thirty-third and thirty-seventh week of pregnancy, between the thirty-eighth week and term, and one week after delivery. The majority of this group were young primigravidas. In the pre-eclamptic and eclamptic groups, fasting blood samples were taken both ante partum and post partum. It was impossible to obtain samples from these women prior to the development of the toxemia. More than one sample was secured whenever possible and in the eclamptic group samples were taken frequently. While all of the pre-eclamptic cases studied were severe, the eclamptic cases have been classified as mild, moderate, and severe.

Table I shows the results obtained in the control patients; Table II those obtained in patients with pre-eclampsia; and Table III those in patients with eclampsia. In the normal gravidas, only two determinations out of 33, or 6 per cent, were above the upper normal limit of 2 mg. In the pre-eclamptic women, 23.5 per cent of the determinations exceeded the upper limit of normal, while in the eclamptic patients, 27.0 per cent exceeded this limit. Among the women with pre-eclampsia, 4 of the 8 showed an elevation above the normal on at least one occasion, while in the patients with eclampsia, 7 out of the 11 showed a similar elevation. It is worthy of note that the average increase paralleled the severity of the disease and that the 2 patients who died showed the highest values.

TABLE I. CONTROL

	26-32	33-37	38-40	POST PARTUM
I.T.	1.44	1.13	0.54	1.20
L.V.	0.26	0.80		0.62
E.B.	0.94	0.28	1.23	2.13
A.L.	0.44	1.30	1.58	0.90
M.B.	1.22	0.49	0.82	1.40
M.K.	1.75	0.68	1.65	1.25
L.M.	0.41	1.77	0.48	1.55
D.C.	1.36			0.05
D.L.	1.36	0.30	0.76	2.26

All determinations are given in mg. of alpha amino-nitrogen of blood.

TABLE II. PRE-ECLAMPSIA

	ANTE PARTUM		POST PARTUM	
L.B.	0.82	0.66	1.01	0.93
L.S.		1.40	1.64	
R.M.		0.55	0.74	
H.B.		2.30	3.30	
H.W.		2.78	1.45	
M.I.		1.02	0.22	
C.F.	1.07	0.91	2.11	
A.N.		1.34	0.90	2.28

All determinations are given in mg. of alpha amino-nitrogen of blood.

The results indicate a tendency toward an increase of the lipid amino-nitrogen of the blood in pre-eclampsia and eclampsia. Charles, Fisher, and Scott<sup>7</sup> have recently disputed the original tenet of Howells that cephalin is the thromboplastic substance. Despite the evidence of these authors, which one of us (M) has partially confirmed,\*

\*Cephalin, prepared according to the method of Levine,<sup>8</sup> does not induce coagulation of peptonized plasma and may be injected intravenously into dogs in doses up to 800 mg. with impunity.

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## THE LIPID AMINO-NITROGEN IN ECLAMPSIA AND PRE-ECLAMPSIA

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THE blood lipids in patients with eclampsia and toxemias of pregnancy have been studied by several investigators.

Lindeman<sup>1</sup> showed that the blood lipids in eclampsia were high while the fats were low. Slemons and Stander,<sup>2</sup> as well as Helmuth,<sup>3</sup> found that there was no significant change in the lipids in whole blood in eclampsia. In an excellent study of the subject Boyd<sup>4</sup> concluded that there was no variation in any single lipid in either the red cells, white cells, serum, plasma, or whole blood, but that there was an elevation in the plasma cholesterol-phospholipid ratio. This change occurred consistently in cases of eclampsia but only very rarely in pre-eclampsia.

There has been no attempt to analyze the individual phospholipids. The present report is concerned with a study of the blood lipid amino-nitrogen in pre-eclamptic, eclamptic, and normal gravid women.

### METHOD

The method of Kirk, Page and Van Slyke<sup>5</sup> for the determination of alpha amino-nitrogen in the alcohol-ether and petroleum ether extractives of whole blood was used. According to these authors the amino group is derived in large part from cephalin

THE CLINICAL SIGNIFICANCE OF PELVIC VARIATIONS\*  
A DIMENSIONAL STUDY OF THE UPPER, MID, AND LOWER PELVIS IN 200  
WHITE PRIMIPAROUS WOMEN

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THE development of precise roentgenometric methods during the past decade has revised our concepts of the architecture of the female pelvis, and has added a diagnostic technique of great practical value to clinical obstetrics. Several methods for roentgen pelvimetry have been described, but some of these are so complicated, and require the use of such elaborate equipment, as to make them unsuitable for use in the average roentgen laboratory. Moreover, in some instances the interpretation of results is an esoteric art which few roentgenologists or obstetricians have the time or inclination to master. These shortcomings have tended to create an impression that roentgen pelvimetry is more properly an exercise of research laboratories than the concern of the practicing obstetrician. The potential usefulness of a roentgenologic survey in the management of individual obstetric cases has not been generally realized.

The method which is briefly outlined in this communication is simple, rapid, and inexpensive, and, during the past four years, it has been used routinely in primigravid patients. The findings in 600 white women were recently published<sup>1</sup> but did not include the routine measurement of the midpelvic plane. In the present series of 200 cases this has been done and the chief purpose of this presentation is to record and analyze the data in this group of patients. As in the previous series, these were primigravid white women consecutively delivered at term (child 2,500 gm. or over) in the wards of the New Haven Hospital. It is our opinion that they present a fair sample of obstetric pelvises in white women and so furnish criteria of normalcy without which abnormalities cannot be properly evaluated. This analysis of pelvic findings will be preceded by a discussion of the obstetrically important pelvic diameters, a brief outline of the technique of pelvimetry and a classification of pelvic variations.

THE IMPORTANT PLANES AND DIMENSIONS OF THE OBSTETRIC PELVIS

From the obstetric viewpoint there are three portions of the pelvis concerning which information is important. These are: (1) The plane of the pelvic inlet, (2) the midpelvic or narrow pelvic plane, and (3) the planes of the pelvic outlet. A

\*The studies from which the conclusions in this paper are drawn were supported by the Research Funds of Yale University School of Medicine.

TABLE III. ECLAMPSIA

		ANTE PARTUM		POST PARTUM			
K.C.	Severe (died)	5.64					
T.R.	Moderate	1.31	2.41	0.40	1.43		
V.R.	Mild			3.61	2.54	1.62	0.79
F.	Moderate	1.73	1.12	0.87	1.92		
M.B.	Moderate			1.60	2.38	2.35	1.08
R.G.	Mild	1.40		1.08	1.82		
C.A.	Severe (died)	3.78	6.42				
E.G.	Mild	1.78		1.06			
J.F.	Moderate	2.70		1.59	0.74		
K.C.	Moderate	1.03	2.21	0.54	1.62		
G.F.	Mild	0.94		1.62			
A.B.	Mild			0.49	0.83	1.41	0.79

All determinations are given in mg. of alpha amino-nitrogen per 100 gm. of blood.

it must be granted that thromboplastin is a substance closely related to cephalin and is in the part of the lipid extractives of blood and tissues which contains amino-nitrogen. The increase of the lipid amino-nitrogen fraction of the blood is of interest in the light of Fahr's<sup>10</sup> conclusion concerning the fundamental lesion in eclampsia, a deposition of fibrin and thrombosis in the smaller branches of the portal veins and in the afferent arterioles of the glomeruli. If the lipid amino-nitrogen fraction of the blood contains the thromboplastic substance, and this is increased in eclampsia, it would be possible to account for the hepatic lesion on the basis of the increased coagulability of the blood. Dieckmann<sup>11</sup> attempted to increase the coagulation time in dogs by the injection of proteins and produced a lesion of the liver similar to, but not identical with that found in women with eclampsia.

On the other hand the increase of the lipid amino-nitrogen may be the result and not the cause of the damage to the liver, a conclusion more in accordance with the findings of Andrus and Moore,<sup>6</sup> who reported a similar increase in obstructive jaundice with severe liver damage. Further conclusions concerning the findings must await more exact knowledge of the nature of thromboplastin and the pathogenesis and etiology of eclampsia.

#### SUMMARY

There is a significant elevation of the blood lipid amino-nitrogen in the whole blood of eclamptic and pre-eclamptic women and the elevation parallels the severity of the toxemia.

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## SUMMARY

We consider the following diameters to be important in routine pelvimetry:

## Pelvic Inlet

Anteroposterior  
Transverse  
Posterior sagittal

## Narrow Pelvic Plane

Anteroposterior  
Transverse (bispinous)  
Posterior sagittal

## Pelvic Outlet

Transverse (bituberal)  
Posterior sagittal

The lengths of these diameters serve as an excellent index of the available space in the bony birth canal and also as a useful record in statistical studies of the pelvis. We wish also to emphasize the importance of certain contours which are visualized in the roentgenograms or ascertained by palpation. As will be noted below, the contours of the pelvic inlet and those of the lateral aspect of the pelvis are readily seen in the roentgenograms.

## METHOD USED FOR ROUTINE PELVIMETRY

The pelvic inlet may be visualized and measured by the centimeter grid method of roentgen pelvimetry.<sup>4</sup> This consists of the projection of the pelvic inlet to the sensitive film with the patient in a semirecumbent position and the target at a 30 in. distance. Distortion due to the spread of the rays is corrected by the perforated centimeter grid which is placed in the plane of the pelvic inlet following the exposure and removal of the patient from the table. A second (flash) exposure reproduces small dots on the film, the distance between which represents centimeters in the plane of the inlet. All of the pelvic inlet diameters may be read directly. In addition, the outline of the inlet may be visualized as well as the side walls of the lower pelvis and the ischial spines. The distance between these processes (bispinous diameter) is also measured on this film, using a distortion table to correct spread of the rays for the level in which they rest. This level is determined in the lateral film.

The second roentgenogram depicts the lateral aspect of the pelvis and is taken with the patient standing laterally to the target which is placed at 5 foot distance. Distortion due to the spread of the rays is corrected by means of an opaque centimeter notched rod which is placed posterior to the patient and in the midplane of the body. A corrected scale is thus projected on the edge of the film and with calipers all of the anteroposterior diameters of the pelvis may be measured. On this film, therefore, we measure the anteroposterior diameter of the inlet, the anteroposterior diameter of the narrow pelvic plane, the posterior sagittal diameter of this plane, and the posterior sagittal diameter of the outlet. Also, in the lateral film we may visualize all of the important lateral contours of the pelvis, including the sacral curve and the character of the sacrosciatic notch.

For the determination of the intertuberal or transverse diameter of the outlet, we depend upon palpation and direct measurement. The contour of the lateral aspects of the pubic arch are also described after palpation. For routine purposes we have found these outlet palpatory methods quite as satisfactory as roentgenometry of this portion of the pelvis.

knowledge of the dimensions and contours of these planes of the pelvis will present useful knowledge of available pelvic space and will furnish an index of the architecture of the pelvis.

*The Plane of the Pelvic Inlet.*—This plane may be described as follows. It is bounded anteriorly by the upper posterior surface of the symphysis, laterally by the iliopectineal lines, and posteriorly by the upper anterior surface of the sacrum at the point where the iliopectineal lines would meet if they were to be continued posteriorly. In the individual pelvis this point may or may not be located at the promontory. It is usually somewhat below this process. It will be seen that the plane thus described is not that of the anatomic superior strait. Its importance as the obstetric inlet of the pelvis has been emphasized by Caldwell, Moloy, and D'Esopo<sup>2</sup> and others.

In addition to a knowledge of the shape of the plane of the pelvic inlet, there are three diameters which furnish useful information: (1) The anteroposterior diameter, (2) the transverse diameter, and (3) the posterior sagittal diameter.

*The anteroposterior diameter* extends from a point on the upper posterior surface of the symphysis about 1 cm. below the superior border to the anterior surface of the sacrum at the point where the iliopectineal lines would meet if they were to be continued.

*The transverse diameter* is the greatest distance separating the iliopectineal lines. It bisects the anteroposterior diameter somewhat posterior to its midpoint.

*The posterior sagittal diameter* is that portion of the anteroposterior diameter which is posterior to the point of intersection by the transverse diameter. It is useful as an index of the amount of space in the upper posterior pelvis. When abnormally shortened, it represents an abnormal posterior displacement of the transverse diameter.

*The Midpelvic or Narrow Pelvic Plane.*—This plane is also known as the plane of least dimensions and has been defined as extending from the lower border of the symphysis laterally through the ischial spines, then posteriorly to the tip of the sacrum. However, as Hanson<sup>3</sup> has pointed out, these points are not truly in the same plane, the tip of the sacrum often being 2 cm. or more below the proper level of the posterior part of such a plane. This author suggests that the posterior limit should be placed at the juncture of the fourth and fifth sacral vertebrae, and our studies of the lateral pelvic aspect have confirmed the soundness of his view.

*The anteroposterior diameter* of the midpelvic plane, therefore, extends from the lower border of the symphysis through the bispinous diameter, and usually to the junction of the fourth and fifth sacral segments. (Rarely this posterior point is subject to variation, especially in sacra containing more or fewer than the usual number of segments.)

*The transverse diameter of the narrow pelvic plane*, also known as the bispinous diameter, is the shortest distance separating these projections.

*The posterior sagittal diameter* of the narrow pelvic plane is that portion of the anteroposterior diameter which lies posterior to its intersection by the bispinous diameter. This diameter gives a useful index to the available space in the posterior lower midpelvis and its length is modified by the size and shape of the greater sacrosciatic notch.

*The Pelvic Outlet.*—The pelvic outlet consists of two planes represented by two triangles, the bases of which join along the line of the bituberal diameter. The anterior triangle is bounded laterally and above by the bones comprising the pubic arch. The posterior triangle is bounded anteriorly by the bituberal diameter and its sides converge posteriorly to the tip of the sacrum. The important diameters of the outlet are the bituberal or transverse of the outlet, representing the widest separation of the lower inner surfaces of the tubera ischii and the posterior sagittal diameter which extends posteriorly from a midpoint on the bituberal diameter to the anterior surface of the tip of the sacrum. Other diameters, such as the anterior sagittal and anteroposterior, have been described as useful pelvic outlet measurements, but in our opinion they are without important obstetric significance.

may affect various portions of the female pelvis. The android characters which may be found at the pelvic inlet are:

1. The curve of the iliopectineal lines is less arcuate and the transverse diameter is displaced posteriorly, thus shortening the posterior sagittal diameter in this plane.

The midpelvic plane may also present certain android characteristics. These are:

1. Decreased width of the side walls of the pelvis resulting in a shortened bispinous diameter.

2. Laterally, the male type or narrow sacrosclatic notch is present. The posterior pelvic capacity of the mid- and lower pelvis is therefore decreased and the posterior sagittal diameter in the midpelvic plane abnormally shortened.

The android changes affecting the outlet are:

1. Narrowing of the pubic arch with less arcuate formation of its sides, and a relative shortening of the bituberal diameter.

2. Shortening of the posterior sagittal diameter of the outlet.

These android characteristics may occur at the inlet, midpelvis, or outlet, and in a certain small group of female pelvises they may occur in all three portions. These changes may have pronounced obstetrical significance, especially in the completely "android" pelvis. When an individual pelvis shows any android or other significant change, this information is incorporated in the basic classification set down above.

An idea of the distribution of these basic pelvic types in white women may be gained from their incidence in our total cases (800):

Dolichopellic	type occurred 129 times or 16.12 per cent
Mesatipellic	type occurred 367 times or 45.88 per cent
Brachypellic	type occurred 272 times or 34.00 per cent
Platypellic	type occurred 32 times or 4.00 per cent

We would again call attention to the fact that 62 per cent of this series present pelvises whose inlet differs markedly from that described as normal in present-day textbooks on anatomy. To those interested in further studies concerning this question, references to recently published articles are given.<sup>5, 6</sup> Attention also is called to the incidence of the platypellic type in but 4.0 per cent of the series. In many of these pelvises the evidence of rachitic influence was notable. It is our feeling that in general the latter type should be regarded as pathologic and therefore considered somewhat differently than the first three groups.

In this group of 200 pelvises, the incidence of pelvic type was as follows:

Dolichopellic,	37 instances or 18.5 per cent
Mesatipellic,	95 instances or 47.5 per cent
Brachypellic,	62 instances or 31.0 per cent
Platypellic,	6 instances or 3.0 per cent

In order to gain some idea concerning the normal range of measurements, certain statistical data in the present series may be interesting. The average measurements for the whole series are:

<i>Inlet:</i>	Anteroposterior	11.6 cm.
	Transverse	12.34 cm.
	Posterior sagittal	4.44 cm.
<i>Midplane:</i>	Anteroposterior	12.25 cm.
	Transverse	10.17 cm.
	Posterior sagittal	5.21 cm.
<i>Outlet:</i>	Transverse	9.05 cm.
	Posterior sagittal	7.84 cm.

Of greater interest are the mean values for the various pelvic types. These are shown in Table I.

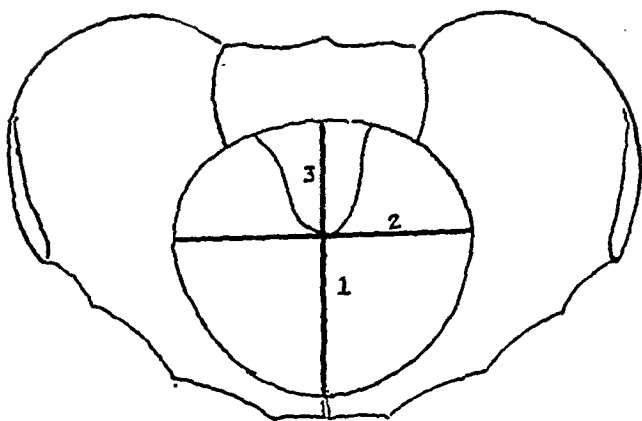


Fig. 1.—Diameters of the pelvic inlet. 1, Anteroposterior diameter; 2, transverse diameter; and 3, posterior sagittal diameter.

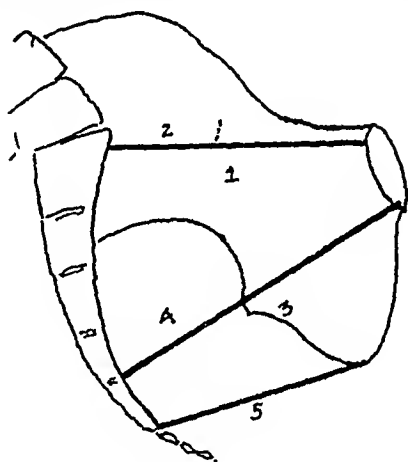


Fig. 2.—Diameters of the lateral pelvis. 1, Anteroposterior diameter of inlet; 2, posterior sagittal diameter of inlet; 3, anteroposterior diameter of midplane; 4, posterior sagittal diameter of midplane; and 5, posterior sagittal diameter of outlet.

#### PELVIC VARIATIONS AND THEIR CLASSIFICATION

The chief contribution of roentgen studies in recent years is the recognition of definite variations in form of the female pelvis. Studies in this clinic and elsewhere have shown that for practical obstetric purposes female pelves may be divided into four general groups using the shape of the pelvic inlet as a basis for classification. The following variations in pelvic inlet conformation may be thus classified:

- I. Dolichopellic or anthropoid type: The anteroposterior diameter exceeds the transverse diameter, the pelvis being elongated anteroposteriorly.
- II. The mesatipellic or round type: The anteroposterior and transverse diameters are of equal length, or the transverse exceeds the anteroposterior by not more than 1 cm.
- III. The brachypellic or oval type: The transverse diameter exceeds the anteroposterior by more than 1 cm. and less than 3 cm.
- IV. The platypellic or flat type: The transverse diameter exceeds the anteroposterior diameter by 3 cm. or more.

In discussing pelvic variations we should not overlook certain changes characteristic of male pelves and spoken of as android changes, which



6. Persistent posterior position, low forceps.
7. Prolonged labor, low forceps.
8. Small pelvis, contracted midpelvis and outlet, low forceps.

*Mesatipellic type:*

1. Cesarean section, persistent face presentation, contracted outlet.
2. Premature separation of placenta, cesarean section.
3. Arrest of posterior position in midpelvis, midforceps.
4. Contracted midplane, posterior arrest in midpelvis, midforceps.
5. Child 4,180 gm., arrest at outlet, low forceps.
6. Normal pelvic dimensions, arrest at outlet, low forceps.
7. Small pelvis, prolonged labor, low forceps.
8. Normal pelvic dimensions, arrest at outlet, low forceps.
9. Small pelvis, low forceps.
10. Prolonged labor, low forceps.
11. Contracted midpelvis, low forceps.
12. Persistent occipitoposterior, low forceps.
13. Small pelvis, low forceps.
14. Outlet contraction, low forceps.

*Brachypellic type:*

1. Essential hypertension with dystrophia dystoeia syndrome, cesarean section.
2. Premature separation of placenta, cesarean section.
3. Contracted midpelvis, contracted outlet, child 3,935 gm., midforceps.
4. Contracted outlet, transverse arrest, midforceps.
5. Child 4,075 gm., small pelvis, contracted midpelvis, midforceps.
6. Child 3,980 gm., prolonged second stage, midforceps.
7. Child 4,135 gm., contracted midpelvis and outlet, midforceps.
8. Rheumatic heart disease, midforceps.
9. Normal pelvic dimensions, arrest in midpelvis, midforceps.
10. Normal pelvic dimensions, low forceps.
11. Contracted midpelvis, low forceps.
12. Contracted outlet, low forceps.
13. Small pelvis, contracted outlet, low forceps.
14. Contracted midpelvis, arrest at outlet, low forceps.
15. Pulmonary tuberculosis, low forceps.

*Platypellic type:*

1. Rachitic pelvis, a.p. diam. inlet 6.0 cm., cesarean section.

If we omit outlet or low forceps in this series of 200 deliveries, we find that operative intervention was necessary 15 times, or in 7.5 per cent. The distribution of these 15 operations was as follows:

Dolichopellic type, 1 operation, or 2.5 per cent
Midforceps, 1 instance
Mesatipellic type, 4 operations, or 4.2 per cent
Cesarean section, 2 instances
Midforceps, 2 instances
Brachypellic type, 9 operations, or 14.5 per cent
Cesarean section, 2 instances
Midforceps, 7 instances
Platypellic type, 1 operation or 16.6 per cent
Cesarean section, 1 instance

As was noted in previous studies, the more serious types of intervention are increasingly necessary in brachypellic or platypellic pelvic types. This re-emphasizes our previous dictum that the most favorable type of pelvic inlet is that which is round or which is elongated anteroposteriorly (mesatipellic or dolichopellic), and not the transversely oval pelvis (brachypellic).

TABLE I

	INLET			MIDPLANE			OUTLET	
	A. P.	TRANS.	P. S.	A. P.	TRANS.	P. S.	TRANS.	P. S.
Dolichopellic	12.53	11.72	5.07	12.55	9.45	5.22	8.95	7.84
Mesatipellic	11.75	12.32	4.48	12.34	10.34	5.23	9.16	7.71
Brachypellic	11.06	12.67	4.15	12.01	10.32	5.23	8.92	8.05
Platypellic	9.0	12.67	2.75	11.67	10.45	4.71	9.12	7.58

Certain conclusions from a survey of this table may be stated. In the dolichopellic type there is a tendency for the anteroposterior-transverse relationship to be maintained throughout the pelvis. In the brachypellic type a similar tendency is maintained, although in a less striking manner. In the platypellic group, the shortened posterior sagittal of the inlet and wide bispinous diameter suggest that rickets plays a role in the etiology of this group. Evidences of the effects of this disease will be found in the sacral contours and sacral positions in many pelves in this group.

For clinical purposes it is useful to establish criteria for the designation of small pelves. Such a designation is necessarily arbitrary and depends upon how far one is willing to stretch the limits of normality. However, if "average" pelves may be defined as those lying within the interquartile range, that is, the middle half of all, then small pelves may be defined as those which are measurably smaller. Using the anteroposterior diameter of the inlet as the yardstick, it is found that for each of the first three pelvic types the lower limit of the average group is 0.5 cm. less than the mean for the type. About one-fifth of all pelves are measurably smaller and are, therefore, designated as "small." By this definition small pelves occur with approximately equal frequency in the three pelvic types as indicated below.

- Dolichopellic type:* Anteroposterior diameter less than 12.0 cm.  
Small pelvis 7 instances or 18.9 per cent.
- Mesatipellic type:* Anteroposterior diameter less than 11.25 cm.  
Small pelvis 17 instances or 17.9 per cent.
- Brachypellic type:* Anteroposterior diameter less than 10.5 cm.  
Small pelvis 11 instances or 17.7 per cent.

In further considering the mean measurements given above it may be clinically useful to construct a table based on the lower limits of normal for each measurement. This has been done in the table below. It is our opinion that dimensions smaller than those given for the various diameters should be regarded circumspectly.

TABLE II

	INLET			MIDPELVIS			OUTLET	
	A. P.	TRANS.	P. S.	A. P.	TRANS.	P. S.	TRANS.	P. S.
Dolichopellic	12.0	11.25	4.5	12.00	9.25	5.0	8.5	7.5
Mesatipellic	11.25	11.75	4.0	11.75	9.75	5.0	8.5	7.5
Brachypellic	10.75	12.25	3.75	11.50	10.00	5.0	8.5	7.5

In considering the clinical relationships of the series (200 pelves), certain interesting facts present themselves. In this group of primiparous patients delivered at term, labor was terminated by operative intervention 36 times, or 18.0 per cent.

A brief analysis of intervention in the series follows:

*Dolichopellic type:*

1. Small pelvis, contracted midplane and outlet, posterior position, midforceps.
2. Small pelvis, contracted midplane, low forceps.
3. Child 3,920 gm., arrest at outlet, low forceps.
4. Child 4,175 gm., arrest at outlet, low forceps.
5. Prolonged labor, contracted outlet, low forceps.

In recapitulation we would state:

I. A knowledge of pelvic variations and of the changes that may affect the conformation of the pelvis as a whole or in part is essential for the practice of scientific obstetrics.

II. In order to recognize such changes a knowledge of the diameters and contours of certain pelvic planes is essential. These planes are the plane of the pelvic inlet, the midpelvic plane, and the planes of the pelvic outlet.

III. A dimensional study of the pelvis for obstetric purposes is possible only by roentgen pelvimetry, and simple and inexpensive methods for its performance are herein briefly outlined.

IV. The results of a pelvimetric survey in 200 white women are presented and from the mean diameters a criterion for "small" pelves may be established.

V. An analysis of operative intervention and of prolonged labor in this series shows that abnormal changes in the pelvis must be reckoned as among important etiologic factors.

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#### CAUDAL ANESTHESIA IN OBSTETRICS\*

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IN OUR approach to an ideal obstetric anesthesia, we have been convinced that DeLee has indicated the right direction by emphasizing the advantages of local or regional nerve block. With the hope of contributing some refinements to the technique of local anesthesia in obstetrics, we have undertaken a study of regional nerve block administered by the caudal route.

Caudal or sacral anesthesia is a type of central nerve block and central nerve block anesthesia in general may be classified into two main types: the *subarachnoid block* or so-called *spinal anesthesia* in which the anesthetic is mixed directly with the spinal fluid, and the *epidural anesthesia* in which the anesthetic agent is deposited extradurally and acts on the nerve trunks in the space between the dura and the outer bony canal of the vertebral column. Caudal anesthesia is a type of epidural anesthesia produced by injecting the anesthetic agent through the terminal central sacral hiatus so that it bathes the terminal branches of the spinal cord, and it is generally believed that the agent confines

\*Read by invitation at a meeting of the Baltimore Obstetrical and Gynecological Society, February 10, 1939.

Another criterion in any study of clinical relationships involving the bony pelvis is that concerning prolonged labor. We are well aware that many factors enter into the etiology of this condition, and among these we recognize the following: (I) Unfavorable aspects of the bony birth canal, (II) oversize child, and (III) unfavorable presentation. In this series of 200 labors 38, or 19 per cent, were of twenty-four hours or more duration. In 28, or 73.7 per cent, one or more of the three factors mentioned was present, and in 22, or 57.9 per cent, the pelvis showed abnormal dimensional changes. A brief analysis of these 28 prolonged labors follows:

<i>Length of Labor</i>		<i>Associated Factors</i>
1.	29½ hr.	Small brachypellic type, contracted outlet, intervention.
2.	41 hr.	Small brachypellic type, child 4,075 gm., intervention.
3.	27 hr.	Dolichopellic type.
4.	27½ hr.	Contracted midpelvis, contracted outlet.
5.	24 hr.	Dolichopellic type, contracted outlet, intervention.
6.	40 hr.	Small mesatipellic type.
7.	32 hr.	Small brachypellic type, contracted midpelvis.
8.	29¼ hr.	Small mesatipellic type.
9.	41½ hr.	Contracted outlet.
10.	28 hr.	Child, 3,980 gm., intervention.
11.	33 hr.	Contracted outlet.
12.	25¾ hr.	Small dolichopellic type.
13.	34½ hr.	Contracted outlet.
14.	24 hr.	Small brachypellic type, contracted outlet, intervention.
15.	30 hr.	Small mesatipellic type, contracted midpelvis intervention.
16.	32 hr.	Contracted outlet.
17.	55 hr.	Contracted midpelvis, contracted outlet, child 4,135 gm., intervention.
18.	31 hr.	Frank breech presentation.
19.	28 hr.	Child 4,090 gm., small mesatipellic type.
20.	48¾ hr.	Child 4,400 gm.
21.	38¼ hr.	Platypellic type, a.p. inlet 9 cm.
22.	33½ hr.	Persistent occipitoposterior, intervention.
23.	50 hr.	Small dolichopellic type, contracted outlet.
24.	70 hr.	Persistent occipitoposterior, intervention.
25.	48 hr.	Small dolichopellic type, contracted outlet, intervention.
26.	30½ hr.	Platypellic type, a.p. inlet 10.0 cm.
27.	48¼ hr.	Contracted midpelvis.
28.	25¾ hr.	Platypellic, a.p. inlet 8.75 cm.

In the table above the incidence of outlet contraction 11 times shows again the importance of this abnormality as a factor in prolonged labor. In 14 instances the pelvic inlet showed dimensions less than normal for the particular type of pelvis and in 5 instances the midplane showed contraction either alone or in combination with contraction elsewhere in the pelvis. In considering both operative intervention and prolonged labor in this series, these findings emphasize the importance of the knowledge which a pelvimetric survey of the whole pelvis furnishes. Furthermore, it seems apparent that unless such a routine survey in primiparous patients is carried out, many significant pelvic changes will remain undiscovered.

In our first dozen or so cases the procedure was attempted immediately post partum on those patients in whom perineal repair was indicated. We followed the technique of administration with the patient in the lateral decubitus, the method which is almost universally advocated. Thirty cubic centimeters of 1 per cent novocaine were used through a 3-inch 20 gauge, spinal puncture needle. Our results were most discouraging. In our first 15 or 20 attempts, we produced satisfactory anesthesia only several times and occasionally only spotty or unilateral anesthesia. In spite of the fact that in many cases the fluid flowed without resistance and there was no tumefaction of the skin overlying the sacrum, we felt that the sacral canal had not been entered. We were about to abandon the procedure as unreliable when we decided to try the knee-elbow position and use a heavier needle. Our percentage of successful anesthetics immediately increased and shortly thereafter we discovered a maneuver by which we believe we can definitely establish the fact that the needle is in the canal before any solution is injected. With the needle inserted well in the canal and the patient in the knee-elbow position, the needle is partially withdrawn and reinserted with simultaneous downward pressure on the hub of the needle, the tip of the needle can be felt to scrape along the anterior surface of the posterior sacral wall which lies above the needle. If this sign is not elicited, the fluid is not injected, under our more recent procedure. We have had no failures in any case in which this sign was elicited.

Our investigations suggest that 30 c.c. of 1 per cent novocaine with 8 minims of 1:1000 adrenalin solution through a  $3\frac{1}{2}$  inch 18 gauge, spinal puncture needle gives results which are the most uniformly reliable, and we have found no advantage in using other agents which are claimed to have a prolonged action. The addition of sodium bicarbonate solution frequently claimed to hasten or prolong the action of novocaine was not confirmed in the few cases in which we have tried it.

#### TECHNIQUE

The technique of administration and the necessary armamentarium which we now use are as follows: The operating room nurse sets up a sterile tray consisting of a sheet 20 inches by 28 inches, in the center of which is a hole  $4\frac{1}{2}$  inches in diameter; a medicine glass containing 30 c.c. of 1 per cent novocaine plus 8 minims of 1:1000 adrenalin; a 10 c.c. Luer syringe; a 25 gauge hypodermic needle; an 18 gauge spinal puncture needle  $3\frac{1}{2}$  inches long and a few gauze sponges. The patient is placed in the knee-elbow position so that the back remains horizontal and the area over the sacral hiatus is cleaned with iodine and alcohol. The operator, by palpation, locates the sacral hiatus. This is identified as a horseshoe-shaped notch or as an inverted V-shaped notch usually about 2 cm. above the junction of the coccyx and sacrum. It should be remembered that the sacral hiatus is found in the midline always cephalward from the sacrococcygeal junction. This is a vitally important rule which will prevent possible disastrous results which might occur if the needle were inserted anterior to the body of the sacrum. A small skin wheal is raised just above the sacral hiatus by injecting novocaine through the hypodermic needle and several cubic centimeters of novocaine are then deposited between the skin and the bony sacrum, in the subcutaneous tissues. The needle is then withdrawn and the slight tumefaction caused by the preliminary injection is pressed away with the operator's finger. Otherwise, the location of the sacral hiatus may be obscured. The spinal puncture needle containing a stylet is then introduced through the skin

itself to the region of the cauda equina below the level at which the subarachnoid space, with its spinal fluid, usually terminates. Our investigations indicate that in this type of administration the anesthetic travels to a considerably higher level, particularly if a high caudal technique is employed or the agent is injected with a moderate degree of pressure. Under such conditions we have been able to produce lower abdominal and pelvic anesthesia identical with that produced by Odom (1936) and others who have administered the agent into the epidural space through the second lumbar interspace.

Caudal anesthesia was first conceived and attempted for clinical use by Cathelin, the French urologist, in 1905 and in 1909 it was first used by Stoekel in Germany in the second stage of labor. Subsequently it was taken up by other German investigators (Schlimpert and Schneider, 1910; A. L  wen, 1910; H. Schlimpert, 1911 and 1913), and more recently reports have come from several obstetric clinics in this country (Meeker and Bonar, 1923; Oldham, 1927; Rucker, 1930), particularly regarding the use of this procedure in operative vaginal delivery. These reports have been favorable except that partial or complete failures have ranged from 20 per cent to 30 per cent.

Our interest was stimulated by this question and a series of 200 cases in which caudal anesthesia was used was subjected to critical clinical analysis at The Baltimore City Hospitals, Obstetrical Division. In this clinic all primigravidas are routinely delivered by episiotomy and elective outlet forceps and a considerable number of plastic operations are done immediately post partum. Such routine procedures seemed appropriate for a study of caudal anesthesia and in addition the series comprises a number of the more major obstetric operations.

Our investigation was directed toward the answers to the following questions: Is the procedure safe for both mother and child? Is the anesthesia produced adequate and what are the advantages, if any? What are the effects upon the progress of labor? What is the most efficient agent? and finally, What is the degree of technical difficulty of administration one should expect?

Using 30 c.c. of 1 per cent procaine hydrochloride as a standard, we have attempted to evaluate the advantages, if any, of several different modifications of the technique, including varying strengths and volumes of solution with and without adrenalin. Several of the proprietary local anesthetics were used, for which the manufacturers claim prolonged anesthesia. Accurate observations were recorded concerning the patient's blood pressure and pulse, onset, distribution, character and duration of anesthesia. If the anesthesia was administered during labor, we also recorded data regarding relief from pain, any changes in the character or frequency of uterine contractions and the changes in cervical dilatation or station of the presenting part with, of course, frequent auscultation of the fetal heart beat. Observations were made regarding perineal relaxation and the character of the third stage of labor. Attention was focused for immediate or remote sequelae in the puerperium, such as tonicities of the uterus and bladder, headache and symptoms or signs referable to the local site of injection.

quently the contractions are weaker, of shorter duration, and less frequent for five or ten minutes following the injection but soon return to their original status except for the absence of pain. Perineal anesthesia follows in the manner described above and the contractions continue painlessly until shortly before the perineal anesthesia begins to wane. As soon as the contractions become painless the patient loses the urge to bear down and there is usually a dramatic change in her countenance from one registering anguish to relief and gratitude. If the anesthesia is administered in the first stage of labor, although painless contractions continue, our experience indicates that the progress of labor will be arrested until the anesthesia wears off in most cases. We have found one type of case to be the exception to this rule. In primigravidas, having hard labor, with the head deep in the pelvis and the cervix thin but only partially dilated, the anesthetic may be administered and completion of cervical dilatation and descent of the head to the perineum may be expected, with complete absence of pain. We have repeated the anesthesia in this type of case to carry the patient through delivery and repair with gratifying results. Spontaneous delivery under the anesthesia is, unfortunately, the rare exception, and aside from the type of case described above, the anesthesia is not administered until the patient is ready for delivery. Preliminary analgesic drugs are no contraindication to the anesthesia, although in our series most of the patients received only preliminary oral pentobarbital, because we felt that we could more accurately evaluate the anesthesia under study if the patient received a minimal amount of other drugs which might mask the picture. The barbiturate analgesia was chosen because of its counteraction to a possible novocaine toxicity.

### RESULTS

In our series of 200 cases we were unable to enter the sacral canal in 14 and these are classified as complete failures. Eleven of these failures occurred in our first 45 cases and only 3 in the last 155 attempts. This point indicates that a certain amount of experience is essential; nevertheless, we believe there is an irreducible minimum of failures comprising very obese patients and those with an abnormal sacral contour. In 4 other cases, in which the canal was definitely entered, the results were only partially satisfactory. In these 4 cases the anesthesia was administered ante partum for delivery. All 4 patients experienced complete relief from pain during contractions but in 2 no perineal anesthesia followed and in the other 2 only unilateral anesthesia of the perineum was obtained. In the remaining 182 cases the anesthesia was classified as successful although in this group supplementary anesthesia was administered 17 times. Most of these supplementary anesthetics were used only during delivery of the head, in the early part of the series, when we began the operation too soon. At this early date we did not realize that occasionally the onset of surgical anesthesia is delayed forty or fifty minutes following the injection.

TABLE I. 146 CASES RECEIVING ANESTHESIA FOR DELIVERY

	NUMBER	EPISIOTOMY	SUPPLEMENTARY ANESTHESIA	SCANZONI MANEUVER	HYSTEROSTOMATOMY
Low forceps delivery	107	103	10		
Midforceps delivery	14	12	1	2	2
Breech extraction	10	8			
Version and extraction	4		3		
Low cervical section	8		1		
Porro section	1		1		
Spontaneous delivery.	2				

to the sacral hiatus until bony obstruction is met. The needle is then placed on an angle of about 10 degrees to 20 degrees with the vertebral column and pressure will now encounter a membranous resistance. The membrane covering the hiatus is pierced and the needle then meets no resistance as it penetrates the sacral canal. The needle is inserted to a depth of about 2 inches, then slightly withdrawn and then re-inserted while downward pressure is made on the hub of the needle. During this maneuver the tip of the needle will be felt to scrape along the overlying bony surface which represents the anterior surface of the posterior sacral wall. If one desires anesthesia of pelvic viscera, the needle should be inserted  $2\frac{1}{2}$  to 3 inches, although occasionally this is not possible in cases where there is a marked curvature of the sacrum and the tip of the needle meets the curving anterior surface of the posterior wall. The stylet is then withdrawn, and if spinal fluid or blood escapes, the injection should not be done. If no fluid returns, the empty syringe is attached and the plunger withdrawn to again test for spinal fluid or a steady return of blood. We frequently suck back a drop or two of blood at this point, but we have found that if there is no steady flow there is no contraindication to injection. Twenty cubic centimeters of the novocaine mixture is then injected slowly and gently—never under

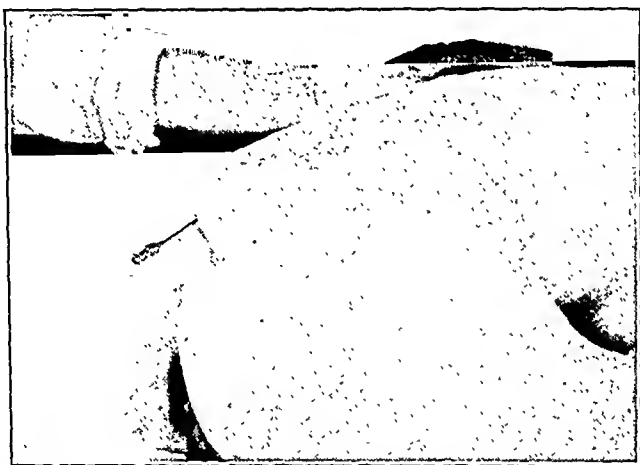


Fig. 1.—Patient in knee-elbow position with needle partially inserted in sacral canal. The caudal drape sheet has been omitted so that landmarks may be correlated.

pressure. It usually flows with very little resistance. Some patients complain of a cramplike pain in one or both legs at this time but this rarely occurs if the injection is done gently. If one is preparing for lower abdominal surgery, the total of 30 c.c. should be injected at this level, but if we are interested only in perineal anesthesia, the needle is withdrawn about 1 inch and the remaining 10 c.c. are injected at this point after the usual precautionary tests are made regarding flow of blood or spinal fluid. This maneuver seems to promote a more rapid onset of perineal anesthesia. Following the complete withdrawal of the needle, the patient is placed flat on her back. About five minutes later the sphincter reflex disappears, and ten to twenty minutes after the injection, anesthesia appears around the anal region and gradually ascends to a varying height, usually well above the level of the symphysis. There is a marked relaxation of the anal sphincter and perineal musculature, and following its onset, approximately twenty to thirty minutes following the injection, surgical anesthesia usually lasts about one and one-half hours and disappears from above downward. There is rarely any sign of motor paralysis although a few of our patients complained of weakness of the legs. Although many patients complain of numbness of the feet and legs the actual anesthesia usually descends only a short distance down the thighs.

If the anesthesia is administered to a patient in labor, the uterine contractions usually become painless immediately, or several minutes, after the injection. Fre-



systemic and 12 points distal. In 2 patients there was an alarming fall in pressure with a classical picture of vascular collapse with a fast, thready pulse and marked anxiety. These patients recovered satisfactorily in about fifteen minutes following abundant and pelvic and perineal anesthesia followed in the usual manner, and they were delivered about one hour later by low forceps and cesarean section, respectively. Both babies were in excellent condition. It seems significant that in both of these cases 2 per cent novocaine was used in doses of 55 cc. and 50 cc., respectively, with the usual addition of adrenalin. We feel that penetration of the dorsal sac or a blood vessel by the needle had been ruled out in these cases before the injection was given. This is a vital point and one must be cautious. In one of our early cases the dorsal sac was entered and clear spinal fluid dropped from the needle when the stylet was removed, before any fluid was injected. The needle was reinserted at a slightly different angle and no fluid could be withdrawn and then the novocaine solution was injected as usual and anesthesia was produced without event. In retrospect, the same procedure and I would hesitate to repeat it. In 1920 Zweifel reported on 4,200 epidural cases operated upon under caudal anesthesia in which 3 deaths occurred shortly after the injection. All 3 deaths were by sudden respiratory failure. As against one 2 of these cases presented definite evidence that the needle had penetrated the dorsal sac and the third case was not investigated.

We have endeavored to determine the distribution of the anesthetic agent by injecting 30 cc. of novocaine colored with methylene blue into the caudal sac of fresh female cadavers, and we have found that with minimal pressure on the syringe the solution distributes itself evenly around the dura in the epidural space up to the eleventh thoracic segment and with only a moderate degree of pressure the solution travels as high as the seventh cervical segment but always extradurally. Walthe (1924) and others have demonstrated that for a comparatively weak novocaine solution the afferent or sensory nerves have a lower threshold for paralysis than motor nerves, and if we accept Osmond's work (1922) which indicates that the afferent nerves from the uterus enter the cord through the eleventh and twelfth thoracic roots in man, then it seems clear that a comparatively weak solution of novocaine distributed evenly in the narrow epidural space as high as the seventh thoracic segment should produce painless uterine contractions and sensory anesthesia of the lower abdomen and pelvis, without motor paralysis. This is exactly what we find clinically by using the epidural anesthesia in contrast to the usual spinal anesthesia in which the cord is bathed in a much greater volume of a stronger anesthetic solution with the consequent sensory and motor paralysis. In one of the 2 anesthetic accidents with vascular collapse mentioned above, in which 50 cc. of 2 per cent novocaine were injected under considerable pressure, sensory anesthesia extended up to about 4 cm. above the xiphoid cartilage but there was, however, no evidence of respiratory embarrassment in either of our cases of vascular collapse, and there was no motor paralysis. It seems likely that if a sufficient number of sympathetic sympathetic fibers are subjected to the action of the comparatively strong solution of novocaine as these fibers pass through the epidural space to the lateral sympathetic ganglia, a sympathetic paralysis with a consequent splanchnic dilatation would manifest itself as a vascular collapse. We feel, on this basis, that no more than 30 cc. of a 1 per cent novocaine solution should ever be used.

Recent investigation (H. Foster and others, 1926) indicates that the distribution of an anesthetic agent mixed with the spinal fluid cannot be accurately regulated in spite of the fact that the relative densities are known and the appropriate position is maintained. With the agent confined in the epidural space, however, this contact with the meninges could not occur because the epidural space terminates superiorly at the level of the foramen magnum where the dura fuses with the bone. The administration of an epidural anesthesia through the caudal sac should, therefore, be done with caution and one must be certain that the needle has not penetrated the dorsal sac before the agent is injected.

To confirm our belief that by using the caudal approach the anesthetic agent confines itself extradurally we first established a sensitive indication test for the pres-

In 146 of the patients the anesthetic was administered antepartum for the delivery of full-term babies. In 123 of these cases an elective episiotomy was performed. In this group there were 107 low forceps deliveries in which 10 supplementary nitrous oxide anesthetics were administered for delivery of the head. There were 14 mid-forceps deliveries including 2 Scanzoni operations and 2 hysterostotomy operations. Breech extraction was performed 10 times and internal podalic version and extraction 4 times. In 3 of the version operations deep ether was administered solely for uterine relaxation as we learned from the first version operation that this procedure cannot be done satisfactorily under the regional block alone, because the contractions are not affected. The group also includes 8 low cervical cesarean sections and 1 porro section. In 3 of these laparotomies supplementary anesthesia was used temporarily when the patient complained during peritoneal traction. The 2 remaining patients in the group were multiparas who delivered spontaneously without pain under the regional anesthesia.

TABLE II. 36 CASES RECEIVING ANESTHESIA FOR PROCEDURES OTHER THAN DELIVERY

	NUMBER	SUPPLEMENTARY ANESTHESIA	APPENDECTOMY
Posterior colporrhaphy	16		
Anterior and posterior colporrhaphy	6		
Repair of old rectovaginal fistula	1		
Dilatation of cervix and uterine evacuation	4		
Laparotomy and sterilization	3	1	1
Multiparas in labor	6		

The anesthetic was administered to 36 patients for procedures other than delivery. This group includes 16 posterior colporrhaphies; 6 anterior and posterior colporrhaphies; 1 repair of an old rectovaginal fistula; 4 cases of instrumental dilatation of the cervix and uterine evacuation; 3 laparotomies for sterilization by cornual resection in one of which an appendectomy was also done. The 6 remaining cases were multiparas who received the anesthetic during the first stage of hard labor but labor was arrested until the anesthesia wore off about two hours later, although painless contractions continued during the period of anesthesia.

The average duration of anesthesia in our series was about one hour forty-five minutes from its onset and the addition of adrenalin to the novocaine seems necessary to attain this duration.

There were no maternal deaths in this series and there was 1 stillborn macerated full-term baby in which the fetal heart could not be heard on admission. All other babies delivered in this series were in excellent condition and cried spontaneously. Blood loss accompanying the third stage of labor was minimal and uterine tonicity maximal. One patient had bladder atony during the first twenty-four hours post partum, requiring catheterization twice. We found no untoward symptoms, such as headache, in the puerperium, and there were no signs or symptoms referable to the local site of injection. One-third of the patients manifested some mild vasomotor disturbances immediately following the injection, principally exhibited by a sensation of chilliness and occasionally a sense of anxiety but these symptoms usually disappeared in about five minutes. Most of the patients revealed a rise in pulse rate immediately following the injection, the average rise being 10 beats per minute although this is difficult to evaluate because the carrying out of the procedure with the assumption of the knee-elbow position, per se, probably contributes somewhat. We carried out the procedure on one patient in active labor and injected 30 c.c. of plain normal saline solution and her pulse rose 20 points. One hundred and six patients had no change in blood pressure whereas in 48 patients there was an immediate rise in blood pressure with the average rise in this group being 20 points systolic and 6 points diastolic. In 2 of these patients there was a transient rise in the systolic pressure of 70 points and in another patient a rise of 100 points, without symptoms. We feel that these changes are referable to the adrenalin used in the mixture. In 27 patients the blood pressure fell, with an average fall of 18 points

obstetrician who prefers a selective policy of anesthesia and endeavors to adapt the anesthesia to a given patient rather than accommodate the patient to any routine anesthetic.

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### THE EFFECT OF PREGNANCY ON GASTRIC SECRETION\*

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**L**OWERED gastric secretion occurring during pregnancy has been designated as one of the possible etiologic factors in the production of anemia during this period.

Nakai<sup>1</sup> (1925), Arzt<sup>2</sup> (1926) and Mason<sup>3</sup> (1931) have reported a high incidence of diminished or absent free HCl during pregnancy. Strauss and Castle<sup>4</sup> (1932) found that 75 per cent of 24 patients did not secrete normal amounts of free HCl or pepsin during more than half of their period of pregnancy. Mettier and Minot<sup>5</sup> (1931) produced evidence suggesting that the acidity of the upper gastrointestinal tract may be of importance in the absorption or utilization of iron compounds.

During the course of recent study of the anemias of pregnancy conducted in Bellevue Hospital<sup>7</sup> (Labate) the state of gastric acidity was investigated. Gastric analyses were performed on 56 pregnant women who entered the hospital during their prenatal period.

#### METHOD OF STUDY

Pregnant women who were referred to Bellevue Hospital during the prenatal period because of false labor, premature rupture of the membranes, or for observation were subjected to a gastric analysis. The analysis was repeated on the eighth day following delivery. All except 2 of these patients had a secondary anemia on admission to the obstetric ward.

No fluid or food was allowed after 9 P.M. of the night preceding the gastric analysis. A Levine tube which was lubricated with mineral oil was passed to the fundus of the stomach, the fasting contents removed, and 300 c.c. of 7 per cent ethyl alcohol instilled. Extractions of the stomach contents were done at fifteen-minute intervals during the next sixty to eighty minutes. If no free HCl was detected after the second specimen following the test meal, 0.3 mg. of histamine was injected subcutaneously. The quantity of free HCl and total acids of each specimen were determined by titration with Topper's solution and phenolphthalein, respectively.

\*This work was carried out by means of a grant from The Bovine Company, Chicago, Illinois.

ence of novocaine in spinal fluid.\* We found that spinal fluid withdrawn by lumbar puncture through the third lumbar interspace from patients under surgical anesthesia up to the level of the umbilicus revealed no trace of novocaine if the anesthetic had been administered by the caudal route. On the other hand, spinal fluid withdrawn in a similar manner from patients with the same level of anesthesia administered as a spinal anesthetic was markedly positive to the novocaine test. These same findings held true even though the dose of novocaine, in milligrams, in the epidural anesthesia was thrice that administered spinally.

#### SUMMARY AND CONCLUSIONS

A clinical study has been made of epidural anesthesia administered by the caudal route, and some refinements have been added to the technique which have enabled us to use this method in a significant number of obstetric cases with successful anesthesia in 91 per cent of the patients.

Our investigations indicate that when administered by the caudal route the anesthetic agent confines itself to the epidural space and travels to a considerably higher level than is generally believed. Our belief has been confirmed by studies on fresh female cadavers which have been injected with colored solutions comparable to those administered clinically. We have also verified the confinement of the agent to the epidural space by finding no trace of the anesthetic in spinal fluid withdrawn by lumbar puncture when anesthesia was present up to the level of the umbilicus.

The advantages of caudal anesthesia are manifold. Pelvic and perineal anesthesia is complete and the uterine contractions become painless and perineal relaxation is marked. Although the urge to bear down disappears there is no motor paralysis and the patient may cooperate by bearing down voluntarily. Uterine tonicity is maximal and thus blood loss is reduced to a minimum. The anesthesia finds its chief usefulness in operative vaginal delivery and spontaneous delivery is the rare exception. The anesthetic may be administered to give an exhausted patient a rest during a protracted labor with gratifying results. In many cases pelvic anesthesia will be sufficiently complete for cesarean section or pelvic laparotomy although, unfortunately, these findings are not constant and cannot be relied upon.

It seems clear that this regional block should be most useful in those cases in which inhalation anesthesia is contraindicated but the widespread routine use of caudal anesthesia would be impracticable and hazardous, because to use the procedure efficiently and safely it is necessary that the operator familiarize himself thoroughly with the technique of administration by training and practice. Many obstetricians could not or would not avail themselves of such an opportunity. The procedure should be of most value in the practiced hand of the

\*We are grateful to the Winthrop Chemical Company for submitting the following test: "To a specimen of spinal fluid (a few cubic centimeters) add several small pieces of ice, 2 drops of dilute hydrochloric acid and 2 drops of sodium nitrite (1:10). Add this mixture to a solution containing 0.2 gm. Betanaphthol in a mixture of 3 c.c. of sodium hydroxide T. S. (normal) and 7 c.c. of distilled water. A scarlet-red to orange-red precipitate results." We have found the test sensitive to novocaine concentrations of 15 mg. per cent.

There appears to be some relationship between the gastric acidity and the level of the red blood count and hemoglobin. The drop in the amount of hemoglobin is noticeable in the patients showing absence of free HCl. However, these average figures are misleading because of the small number of cases in the last 2 groups. For example, in the group showing normal acidity the range of the red blood count was 2.67 to 4.1 million and of the hemoglobin 7.5 gm. to 12.77 gm. There were 3 patients in this group who had a red blood count below 3 million, and 4 of these women had a hemoglobin less than 8.7 gm. The 9 women who showed hypochlorhydria had red blood counts ranging from 2.69 to 4.3 million and hemoglobin ranging from 8.0 gm. to 11.6 gm. In the group having achlorhydria the red blood count ranged from 1.35 to 3.9 million and the hemoglobin from 4.9 gm. to 8.7 gm.

An increase in the average red blood count and hemoglobin occurred on the eighth day post partum in all three groups. The rise was most noticeable in the group showing ante-partum achlorhydria, there being an increase of 0.28 million in red blood cells per c.mm. of blood and 2.87 gm. in hemoglobin per 100 c.c. of blood.

#### DISCUSSION

All except 4 of the 56 patients studied were in the last trimester of pregnancy. Thirty-five were in the last month of pregnancy. Perhaps this may account for the large number (75.0 per cent) of the patients showing normal gastric acidity. Strauss and Castle<sup>5</sup> in a study of gastric secretion on 24 patients during pregnancy reported a 50 per cent decline in maximum free acidity from the third to the sixth month with a rise in the last month to the level observed in the third month. They found that 18 of these patients showed hypochlorhydria during most of the period of pregnancy and only 6 were within the normal range of gastric acidity.

Nakai<sup>1</sup> obtained an average free acidity of 22 c.c. during the first half and 27 c.c. during the second half of pregnancy among 14 patients. Arzt<sup>2, 3</sup> found an acidity in 5 pregnant women during the first trimester and an average of 11 c.c. N/10 HCl per 100 c.c. of gastric juice in 13 others. In a later investigation in which he studied 50 pregnant women, he found 29 lacking free HCl during the first trimester, 6 of whom showed an average of 11 c.c. in the last trimester. Mason<sup>4</sup> studying 4 patients reported hypochlorhydria in 2 with an average of 8 c.c. during the first trimester.

Mettier and Minot<sup>6</sup> made observations which suggest that anemia may result from failure, over a prolonged period of time, in adjustment of the contents of the upper gastrointestinal tract to a pH more suitable for iron utilization. Their findings indicate that iron compounds are absorbed more readily from the gastrointestinal tract or are utilized more readily for blood formation when administered with an acid than with alkaline meals.

Strauss and Castle<sup>5</sup> made observations which suggested to them that the hypochromic anemias of pregnancy are due either to a direct dietary deficiency or to a deficiency conditioned by gastric anacidity, hypoacidity or associated defects in the presence of fetal demands for blood building materials. The macrocytic anemias of pregnancy they thought to be due to a temporary lack in the gastric juice of the specific intrinsic factor which has been shown to be absent from the gastric juice of patients with Addisonian pernicious anemia in relapse.

At present this report indicates that no precise correlation should be made between the acidity of the upper gastrointestinal tract and the development of the secondary anemias of pregnancy. Fifty-four of the patients studied were found to have a secondary anemia at the time that the gastric analyses were done during the ante-partum period. One

## RESULTS

Fifty-six gastric analyses were performed. Thirty-five of the analyses were done on patients during their last month of pregnancy; 13 analyses were done during the period of pregnancy ranging between thirty-one and thirty-five weeks; 4 between twenty-seven and thirty weeks; 2 during the twentieth week; 1 during the twelfth week; and 1 during the tenth week.

The normal lower limit of free HCl was established at 20 c.c. N/10 acid per 100 c.c. of gastric juice. Patients having a free HCl concentration of less than 20 c.c. N/10 acid per 100 c.c. of gastric juice were considered to have hypochlorhydria. The third group consisted of those patients who showed persistent achlorhydria following the injection of 0.3 mg. of histamine.

Forty-two (75 per cent) of the women studied were found to have normal concentration of free HCl and of total acid in the gastric juice. Nine (16 per cent) possessed less than 20 c.c. of N/10 free HCl per 100 c.c. of gastric juice. Five in this latter group had less than 10 c.c. of N/10 free HCl per 100 c.c. of gastric juice. Five (9.0 per cent) showed posthistamine achlorhydria. One of the 5 patients, showing a complete absence of free HCl, had a macrocytic hyperchromic type of anemia, while the others had a hypochromic anemia.

Two of the patients who were found to have hypochlorhydria during the twentieth and thirty-second week, respectively, developed normal concentration of free HCl later in pregnancy, the former during the thirty-second week and the latter during the thirty-fourth week. A third patient who had normal concentration of free HCl in the twenty-ninth week continued to secrete a normal amount during the thirty-sixth week of pregnancy. A fourth patient persistently showed achlorhydria from the thirty-fourth to the thirty-seventh week of pregnancy, the analysis being performed at weekly intervals.

The group of 42 pregnant women possessing normal gastric acidity had an average maximum concentration of free HCl of 48.88 c.c. and an average maximum total acidity of 59.3 c.c. The range of free HCl in this group was 20 c.c. to 128 c.c. and of the total acid 25.8 c.c. to 142 c.c. Twenty-seven of these patients were in the period of pregnancy ranging between thirty-six and forty weeks; eleven were between thirty-one and thirty-five weeks; 3 between twenty-seven and thirty weeks; and 1 in the twentieth week. The gastric analyses were repeated on 21 of these women in the eighth day post partum. These patients were found to show normal gastric acidity in the post-partum period.

The 9 women with hypochlorhydria had an average maximum free HCl of 10.2 c.c. and an average maximum total acid of 27 c.c. The range of free HCl was 5.4 c.c. to 18 c.c. and of total acid 10 c.c. to 33.6 c.c. Six of these patients were in the period of pregnancy ranging between thirty-six and forty weeks; 2 in the thirty-second week and 1 in the twentieth week. Gastric analyses were repeated on 4 of these patients on the eighth day following delivery. They showed a complete return to normal levels of gastric acidity.

One of the 5 patients showing total posthistamine achlorhydria was in the fortieth week of gestation. A second patient received a gastric analysis during the thirty-sixth week and a third patient during the twenty-eighth week. Two other patients had their gastric analysis on the twelfth and tenth weeks, respectively. Gastric analyses were repeated on the eighth day following delivery on 2 of these women. One showed a return to normal acidity while the other was found to have 10 c.c. of free HCl and 15 c.c. of total acid, per 100 c.c. of gastric juice.

The sample is not sufficiently large among the groups showing anacidity to justify any positive conclusions concerning the effect of gastric acidity on hematopoiesis. Fifty-four of the 56 patients studied were found to have a secondary anemia at the time that the gastric analysis was done. The 42 patients showing normal gastric acidity during the ante-partum period had an average red blood count of 3.60 million and an average hemoglobin (Sahli) of 10.23 gm. The group showing hypochlorhydria had an average red blood count of 3.50 million and an average hemoglobin of 10 gm. The 5 women showing achlorhydria had an average red blood count of 3.10 million and an average hemoglobin of 6.63 gm.

# RUPTURE OF PELVIC INFLAMMATORY MASSES INTO THE URINARY BLADDER

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ON THE Gynecological Service of Harlem Hospital, pelvic inflammatory diseases comprise more than 60 per cent of the admissions. When one considers the frequency of inflammatory masses and tubo-ovarian abscesses, it seems remarkable that more of these do not rupture into the bladder and produce a fistulous communication. Rupture of a pyosalpinx into the urinary bladder has been reported only once before from this hospital.<sup>1</sup>

## PATHOLOGY

If the pathologic anatomy of the infected tubes is taken into consideration, one can readily understand why rupture of a pus tube into the bladder occurs so rarely. Most tubal inflammatory masses lie behind the uterus. It is only rarely that a pus tube is observed lying on top, in front of the uterus, or adherent to the anterior abdominal wall or bladder. In these cases, the original infection, usually gonorrheal, occurs while the tube is anterior to the uterus, and the pus exuding from the fimbriated end of the tube causes a localized peritonitis. As a result, the fimbriated end of the tube becomes adherent to the bladder in the same way that it may become adherent to the ovary or broad ligament. If the infection "clears up," nothing further occurs except adhesion of the fimbriated end of the tube to the bladder. If re-infection occurs, and a pus tube forms, the bladder wall becomes part of the abscess wall. The inflammatory process may invade the bladder wall itself, producing a tubovesical abscess which under certain conditions may rupture into the bladder.

Another type of pelvic inflammatory mass which may rupture into the bladder is found in the postabortal parametric cellulitis. Here the infection leaves the uterus via the lymphatics of the broad ligament forming an exudate between the layers of the broad ligament or the cellulitis may go posteriorly and infringe upon the rectum, or anteriorly and involve the bladder wall. If it extends anteriorly, and the abscess infringes on the bladder, it may ultimately rupture into the bladder.<sup>2</sup>

According to Huet all pelvic inflammatory masses open into the bladder in one of two ways. (1) Rupture. This occurs in the "cold" type when there is a large abscess in the subacute or chronic stage, with marked thinning of the bladder wall. Rupture into the bladder occurs as a result of trauma, a direct blow on the abdomen, coitus, or a too rough gynecologic examination. (2) Perforation. This occurs with an acute abscess, the fistula being established by the gradual extension of the inflammatory process from the abscess cavity, through the various coats of the bladder wall until, finally, the mucous membrane gives way, and there is drainage of the abscess into the bladder.

## PREMONITORY SYMPTOMS

These are difficult to define. As a rule most patients with pelvic inflammatory disease (except postabortal parametritis) present urinary symptoms such as urinary frequency, urgency, burning, etc. However, should a patient with pelvic inflammatory disease have involvement of the bladder wall, it is very difficult to state whether

patient developed a hyperchromic macrocytic anemia in the twenty-eighth week of gestation. She was found to have achlorhydria. Recovery was complete during the post-partum period with return of the gastric acidity to normal. Four other patients having achlorhydria had hypochromic anemias of pregnancy. Lowered gastric acidity may accentuate an anemia which results from factors other than altered gastric acidity, by making difficult the absorption or utilization of iron. This would explain the average lower levels of the red blood count and hemoglobin found in the pregnant women showing hypochlorhydria and achlorhydria.

#### SUMMARY AND CONCLUSIONS

1. Gastric analyses were done on 56 women during pregnancy.
2. Forty-two (75.0 per cent) showed normal gastric acidity. Nine (16.0 per cent) showed hypochlorhydria; and 5 (9.0 per cent) showed complete post-histamine achlorhydria.
3. Fifty-two of the patients studied were in the last trimester of pregnancy, 35 of these being in the last month of pregnancy. Two patients were in the fifth month of pregnancy, 1 was in the twelfth week, and 1 in the tenth week.
4. The average red blood count and hemoglobin showed a decrease as the gastric acidity diminished. This, however, should not be taken as proof that the altered gastric acidity is the main factor in the production of the hypochromic anemias of pregnancy.

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Jahnel, F.: The Resistance of Human Spermatozoa to Extreme Cold, Klin. Wchnschr. 17: 1273, 1938.

Human spermatozoa are capable of reactivation in spite of exposure to extremely low temperatures. A certain definite percentage of those so exposed resume their normal motility when the temperature is returned to normal. The author exposed spermatozoa to temperatures of minus 196° C. for periods varying from four to fifty-two hours, by means of liquid nitrogen. Others were kept at minus 79° C. for forty days and a final group were exposed to minus 269.5° C. by means of liquid helium for five-hour periods. Following each of these experiments a small percentage of spermatozoa became actively motile again.

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## REVIEW OF CASE HISTORIES FROM THE LITERATURE

Di Palma and Stark, in 1929, made a comprehensive survey of the literature up to that time with abstracts of 33 cases. The following cases have been gathered from the literature since then

AUTHOR	AGE	HISTORY	GYNECOLOGIC FINDINGS	TIME OF RUPTURE	CYSTOSCOPY	TREATMENT	RESULT
Molino Boero Chacon	19	Attempted induced abortion with catheter 5 days prior to admission	Bilateral adnexal masses	5 weeks after admission	11 weeks after admission edema near left urethral orifice with healed scar in center	Conservative	Cured
Molino Boero Chacon	45	Attempted induced abortion with catheter 3 days prior to admission	Large left adnexal mass	6 days after admission	Small deep opening surrounded by an area of edema 1 cm. above left urethral orifice	Conservative	Cured
Caporale		Left lower quadrant mass and pain since delivery several years ago			Walnut size area of bulbous edema on the body of bladder from center of which exuded pus	Conservative	Cured
Acs	31	3 year history of P.I.D. following delivery	Large mass right adnexa	3 months after admission urine suddenly contained foul blood and pus		Conservative	Cured
Acs	34	Urinary symptoms following spontaneous miscarriage	Left parametrial mass			Conservative	Cured
Acs	24	Abdominal pain and fever following dilatation of the cervix—3 months prior to admission	Bilateral masses	4 days after admission gross pyuria occurred		Conservative	Cured
Acs	39	Chills, fever, abdominal pain dysuria—6 weeks	Bilateral moderately large adnexal masses		Localized area of edema posterior bladder wall abdominal pressure caused pus to exude from center of this area	Conservative	Cured
Acs	24	Fever and urinary symptoms following spontaneous abortion 1 year ago	Fair-sized mass fixed to right pelvic wall		Entire bladder wall congested, area of edema and perforation behind the right ureter	Conservative	Cured

the bladder symptoms are due to the basic gynecologic condition or to the involvement of the bladder wall. Associated chills and high fever may be present due to the underlying pelvic pathology.

The severity of the local symptoms varies with the extent and location of the involvement of the bladder wall; the bladder is very resistant to contiguous inflammatory conditions. As a result, the exudate may not invade the bladder cavity itself, it may only invade the bladder wall to the mucosa with the production of severe urinary symptoms. The closer the inflammatory exudate to the bladder base, neck, and trigone, the more severe are the symptoms. Intravesical evidence of the perivesical inflammation varies with the type and extent of the latter. If frequent investigations of the urinary tract are carried out, and careful examinations of the urine made, an impending rupture of a perivesical abscess into the bladder may occasionally be anticipated.

Before rupture takes place there is usually an infiltration of the bladder wall, with a gradual diffusion of the exudate from the outer coats through to the mucosa with marked edema of the latter. If a patient, with a pelvic inflammatory mass, shows a localized area of bullous edema on the roof or posterior wall of the bladder, the possibility of impending rupture should be considered.

#### SYMPTOMS OF RUPTURE

The onset of the rupture may be so insidious that there is barely any change of symptoms from those of the prodromal irritative cystitis, to the actual cystitis caused by the pus. On the other hand, it may be very acute; the patient may have voided a clear urine and five minutes later, without experiencing any pain, she may have the desire to urinate again and pass several ounces of pure pus. The patients may experience a feeling of "something giving away."

#### SYMPTOMS AND SIGNS OF ASSOCIATED CONDITIONS

The symptoms of the pre-existing pelvic inflammatory disease, salpingitis, or postabortal cellulitis, may vary with the extent and acuteness, or chronicity of the underlying pathology. Usually these patients are acutely ill with high temperature and chills. The pelvic abscess itself is usually quite large, painful, and extremely tender.

#### DIAGNOSIS

The sudden onset of cystitis, with large quantities of pus in a urine which had previously been fairly clear, in a patient acutely ill with a pelvic inflammatory disease, whose temperature descends by crisis, suggests the diagnosis. Cystoscopic examination at this time establishes the diagnosis. The bladder picture seen in these cases is quite typical. The bladder is filled with large or stringy pieces of pus, so dense that repeated irrigations are necessary before clear visualization can be obtained. (An important differential point is that the flocculent shreds of pus seen in the bladder in this type of cystitis are too large to have been ejected from the ureters.) The area surrounding the fistula is usually the site of a bullous edema, a cobble-stone arrangement of very small, translucent, or reddish cysts, the cysts varying in size from a millimeter to several centimeters. From the center of this edematous area, strings of yellowish or whitish exudate may be seen dripping into the bladder, intermittently or continuously. Pressure on the inflammatory mass, through the lower abdomen causes an increase in the flow of pus. Visualization of the actual perforation is difficult, as this lies deep in a craterlike area caused by the edema and hyperanemia of the surrounding tissue. The entire picture is that of an inverted volcano. In cases of rupture of a cold abscess the fistula may be visualized because of the absence of edema and signs of acute inflammation in the bladder wall. It has been described as a pin-point opening, surrounded by a small area of hyperemia.

Various authors have suggested the injection of lipiodol or dyes into the area of suppuration as a means of confirmation of the diagnosis. The use of lipiodol, or other contrast medium, to establish the diagnosis seems fraught with danger,

in the face of an active suppurative process. Acute exacerbation of the infection may frequently follow this procedure. The history and the cystoscopic picture should be sufficiently clear to establish the diagnosis without further aid.

### PROGNOSIS

The prognosis is favorable but the course may be protracted, ranging from one to six months, depending to a large extent upon the underlying pathology and how rapidly it recedes, either spontaneously, under local treatment, or through surgical intervention. In those instances where a mortality has been reported, as a rule, it has been due, not to the rupture of the abscess into the bladder but to the severity of the underlying pathology.

### TREATMENT

Treatment is divided into three parts:

#### *A. Prophylaxis.*—

All patients presenting pelvic masses associated with urinary symptoms should be carefully observed and have repeated cystoscopic and urine examinations. When cystoscopic evidence of impending rupture presents itself, active treatment directed to the underlying pathology should be undertaken to prevent rupture (surgical treatment).

#### *B. Active Treatment.*—

##### *1. Local.*

##### *2. General:*

The treatment of the bladder following rupture of the abscess is the same as that used in acute cystitis. An indwelling catheter may be used until the acute symptoms have subsided to avoid the necessity of too frequent catheterization. The bladder is irrigated with the usual urinary antiseptics; silver nitrate 1:4000; boric acid, 4 per cent; acriflavine, 1:5000; and instillations of 10 per cent argyrol; or a combination of any of these. It is very important to start the bladder irrigations early as the bladder rapidly becomes filled with pure pus, and the possibility of reflux drainage into the kidney pelves must be considered. Early drainage of the abscess, should be carried out either by colpotomy or extraperitoneal incision. The opening in the original abscess must be free so that the pus will flow through the drainage tract rather than into the bladder.

General treatment consists of rest in bed, douches, short wave therapy, Elliot therapy, sedatives.

#### *C. Late Treatment.*—

This consists in the removal of the underlying infection. In postabortal infection the exudate may subside spontaneously or may require extraperitoneal drainage. If due to pus tubes, these may be removed when Simpson's rules are complied with (absence of temperature for three weeks, etc.). When these tubes are removed, as a rule it is not necessary to repair the bladder at the site of rupture. However, in several cases reported from the literature, the location of the bladder communication was found and closed during the laparotomy for the removal of the adnexal masses. This has not been necessary in any of our cases.

### PERSONAL CASES

CASE 1.—L. J., aged 33, colored, para 0, gravida 0, was admitted to Harlem Hospital, April 10, 1936, with a three weeks' history of constant pain in the left lower quadrant, accompanied by high temperature and chills. She had marked dysuria for two weeks previous to admission and a severe chill the night before. Patient appeared acutely ill. Temperature was 103° F., pulse, 152. Abdomen was distended and rigid, and a hard, irregularly nodular mass was palpated in the lower abdomen, extending to just below the umbilicus. Vaginal examination revealed a large mass filling the pelvis and lower abdomen. Urinalysis showed many clumps of pus cells,

Babies	31	Right lower quadrant pain, fever, urinary frequency	Adnexal mass right lower quadrant	Few days after admission pyuria with remission of symptoms	Conservative	Cured
Babies	30	Chills, fever following an induced abortion 3 years ago	Left adnexal mass, myoma of uterus		1. Hysterectomy 2. Left salpingo-oophorectomy 3. Closure of bladder fistulas	Cured
Babies	20	Pain in left kidney region and abdomen; chills, fever following delivery three months ago	Bilateral parametritis		Conservative	
Fagerstrom	28	11 year history of P.I.D. following induced abortion—past 6 months urinary symptoms with pyuria	Right tubo-ovarian abscess	6 months prior to admission	1. Right salpingo-oophorectomy 2. Closure of bladder fistulas	Cured
Ottow		Normal delivery 6 months prior to admission	Bilateral adnexal masses		1. Hysterectomy 2. Bilateral salpingo-oophorectomy 3. Closure of bladder fistulas	Cured
Ottow	48	Recurrent pain, fever and pyuria	Bilateral adnexal masses		Refused operation	Cured
Sorrentino	28	Recurrent pain, fever and urinary tenesmus	Very tender mass the size of a fist in right fornix	Shortly before admission	1. Appendectomy 2. Right salpingo-oophorectomy 3. Resection bladder wall	Cured

Reports 6 cases, 5 following postabortal parametritis and one following gonorrheal pyosalpinx. 4 patients were treated conservatively. one patient by anterior colpotomy and one patient by laparotomy and colpotomy.

area there was an old blood clot, apparently covering a small excavation. Due to the tremendous amount of purulent flocculi visibility was greatly impaired. After thorough irrigation, it became apparent that the source of the pus on the floor of the bladder was from a fistulous opening in the roof of the bladder. Strings of pus, were seen hanging from the roof and constantly dripping to the floor of the bladder.

*Diagnosis.*—Rupture of a pyosalpinx into the bladder.

Colpotomy (anterior) was performed the following day. A large soft, yielding mass was felt in the anterior cul-de-sac, extending to the right side. Incision with scissors was made at the cervicovaginal junction anteriorly. The anterior vaginal mucosa was separated from the cervix. Separation of a plane of cleavage in this space opened into an abscess from which almost 350 c.c. of very foul-smelling pus escaped. A self-retaining catheter was inserted into the bladder, and two rubber drains into the abscess cavity. Three days after operation the patient's temperature became normal and there was a marked diminution in symptoms.

On June 15, 1936, seventy-three days after admission, patient was discharged at her own request. At this time the urine still showed a few pus clumps, the temperature was normal, but a mass was still present in the center of the abdomen.

The patient was seen again on July 8, 1937, at which time her only complaint was incontinence. Cystoscopy on this date showed a small opening about the size of a pea just posterior to the interureteric ridge in the midline. The rest of the bladder was apparently normal. Attempt to pass a ureteral catheter through this opening was unsuccessful. Indigo carmine, intravenously, appeared in five minutes in the vagina, the source of which was definitely from the old anterior colpotomy wound.

CASE 3.—R. B., white, 32 years old, married fourteen years, para i, gravida 3, was admitted to French Hospital on Aug. 1, 1938, with a four months' history of severe pain in right lower quadrant following an abortion.

The patient appeared acutely ill, temperature 103° F., pulse 130. There were marked tenderness and slight rigidity in the right lower quadrant.

Vaginal examination: External genitalia normal. Cervix in axis of vagina. Uterus normal size, and in good position. A large fluctuant mass filled the right anterior fornix. Posterior cul-de-sac and left fornix clear. Laboratory findings: Urine negative except for few white blood cells. Repeated blood cultures were sterile. Blood count: red blood count, 3,350,000; white blood count, 11,600; polymorphonuclears, 70 per cent; Hb, 60 per cent; lymphocytes, 30 per cent.

Temperature fluctuated from 99 to 102° F. until operation on August 18.

*Preoperative Diagnosis.*—Pelvic abscess. Parametrial postabortal. Just prior to doing a colpotomy the patient was catheterized and pure pus was obtained from the bladder. An anterior colpotomy was performed, opening an abscess between the bladder and the lateral pelvic wall. Several ounces of pus was obtained. A drainage tube and one piece of vaginal packing were inserted. Smears from the abscess showed pus cells, and gram-negative diplococci. Culture showed gram-positive bacilli and diplococci. The immediate preoperative catheterized urine examination was very significant as a urine examined earlier that day on the ward was negative. It was obvious that the abscess had ruptured into the bladder while the patient was being taken from the ward to the operating room. Within a week, following the colpotomy the urine became fairly clear though still containing considerable pus cells and within two weeks, only a few pus cells were found per high power field.

Temperature rose to 105° F. following operation but readily receded, and the patient was discharged in three weeks with a negative urine and a mass still present in the right fornix.

## CONCLUSIONS

1 Spontaneous rupture of pyosalpinx or pelvic abscess into the bladder occurs.

2. The symptoms and signs are usually masked by the underlying pathology. Rupture of a pelvic inflammatory mass into the bladder is usually shown by the sudden appearance, or marked increase of pus in

about 100 white blood cells per high power field, and albumin, three-plus. Blood count: Hb, 55 per cent; red blood count, 3,210,000; white blood count, 34,700; Polymorphonuclears, 90 per cent; stools: negative; Aschheim-Zondek, negative; blood Kahn, three-plus. Blood cultures were repeatedly negative.

A diagnosis of fibroid uterus and left pyosalpinx was made. The patient was given daily bladder irrigations of 4 per cent boric acid, and instillations of 10 per cent argyrol. Seven and a half grains of urotropin, 5 gr. of acid sodium phosphate, and 15 min. T.I.D. tincture of hyoseyamus were administered orally. During the next three weeks she was given three blood transfusions of 500 c.c. each. The temperature varied from 100 to 103. At the end of this time the patient's condition was much improved. Spontaneous rupture of the inflammatory mass into the bladder must have occurred toward the end of the second week in the hospital, as the report of the urine shows there was a marked increase of pus in the urine for several days with an improvement in the patient's general condition.

Cystoscopy was deferred until May 7. A No. 24 cystoscope was easily introduced. Bladder capacity was limited (about 150 c.c.). The bladder contained many flocculi and a tremendous amount of exudate, with particles that were too large to have come through the ureter. The urethral orifices were normal in appearance and location. There was a general hyperemia of the entire bladder mucosa with dimming of the blood vessels. A large area of bullous edema was seen at the junction of the roof and the posterior wall of the bladder, with considerable bulging of that region into the bladder. After thorough irrigation pus was found to be dripping from this area to the floor of the bladder, just posterior to the trigone. Otherwise the roof and sides of the bladder were normal. Indigo carmine injected intravenously appeared in normal time and concentration from both ureters.

*Diagnosis.*—Acute cystitis. Rupture of pyosalpinx into the bladder.

Examination on July 1, 1936, showed the mass to be three fingerbreadths below the umbilicus. A large left adnexal mass was made out vaginally. The right adnexa felt normal. On July 22, the one hundred and fourth day of hospitalization, the patient was discharged to return at a future date for surgery. Temperature was normal for over a week previous to discharge. Urine at the time of discharge showed a few pus clumps and only 10 white blood counts per high power field.

CASE 2.—J. S., colored, 33 years of age, para i, gravida i, was admitted to Harlem Hospital on April 3, 1936, with a three months' history of severe generalized abdominal pain.

Patient appeared acutely ill. Temperature 106.6° F.; pulse, 134. The abdomen was distended, tender, and moderately rigid, particularly in the right lower quadrant. A large mass could be palpated in the lower abdomen extending up to the umbilicus. Vaginal examination revealed a thick, creamy discharge, and verified the tender mass filling the entire pelvis. It was impossible to outline the uterus. Urine examination, few white blood cells per high power field. Albumin three-plus. Blood count: Hb, 55 per cent; red blood count, 4,500,000; white blood count, 8,650.

A diagnosis of a ruptured or leaking pyosalpinx was made. The patient was given an infusion of 1,000 c.c. of 5 per cent glucose in saline and a Harris drip. For a month following admission, patient showed signs of lower abdominal peritonitis, but at the end of this time, temperature had receded to 102° F. and pulse to 120. On May 7, 1936, her urine suddenly showed a marked increase in white blood cells with large clumps and shreds of pus. On May 27 urinary symptoms were diminished, although the urine still showed large amounts of pus. Cystoscopy on this date was reported as follows:

Caliber of urethra very small. Smallest Hanks dilator, No. 11, could not be inserted. Under evipal anesthesia, the urethra was dilated to admit a No. 18 dilator. A No. 24 cystoscope was then easily introduced but had to be depressed downward and backward, with the eye piece upward and almost against the left thigh, at an angle of 90 degrees, as the bladder was markedly distorted and pushed to the right. The entire bladder mucosa was edematous and hyperemic, neither the blood vessels, trigone, nor ureteral orifices could be made out. On the floor of the bladder, posteriorly, there was a localized mound of white which appeared to be pus. There was a bulging area of bullous edema on the roof of the bladder; in the center of this

of the gravest concern. Discussions on this subject are conspicuous by their absence in the literature. Bumm<sup>1</sup> in his textbook on obstetrics devotes one sentence to the subject. He says, "Labor in this type of uterus is apt to be complicated." DeLee,<sup>2</sup> Williams,<sup>3</sup> Bland<sup>4</sup> and Sehumann<sup>5</sup> all mention the deformity but do not discuss adequately its clinical significance. In 1924 I<sup>6</sup> called attention to this subject in a paper read at a meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons. At that time I stressed the dangers to the baby that might occur, especially during labor. I described the complications in the relatively few cases I had observed and made certain recommendations based on these observations. Since that time we have carefully observed and recorded the labors of a considerable number of women who have presented this abnormality, and wish to present the results of this study.

It should be noted that at one stage of development all uteri are bicornuate. The normal process of fusion of the two horns to form a pear-shaped organ results, when carried to completion, in the formation of a uterus well adapted to carry out its part in the process of reproduction. When the fusion is interfered with, the result is an inferior organ frequently incapable of performing this duty normally. The functional deficiency varies directly with the degree of deformity.

The etiology of this deformity is totally unknown. What influences the arrest in development of the uterus can only be surmised. Since it is highly probable that the development, growth, and functional activity of the uterus are so directly under the influence of the hormones, it would seem that a failure of the body to supply these hormones in the proper amount and at the proper time in intrauterine life might be the principal cause responsible for the improper fusion of the two halves of the uterus, as well as for other developmental deficiencies in the organ that may explain certain clinical phenomena mentioned later.

Clinically, the condition can be diagnosed in the early weeks of pregnancy. As a rule the uterus will appear larger on one side than the other. Frequently the development of the body of the uterus will be eccentric. One side will grow much faster and be softer than the other. The smaller horn may present at term merely as a nodule on the surface of the hypertrophied side containing the pregnancy, and has often been mistaken for a fibroid. This is frequently associated with lateral deviation of the body of the uterus toward the side of the hypertrophied horn. Often seven-eighths of the uterus will be found to the right or left of the midline. In other cases the two sides of the uterus seem to hypertrophy at about the same rate and at term the fundus of the uterus instead of being rounded, presents a groove or notch on its upper aspect with the horns on each side. The width of the fundus in these cases is greater than normal.

I have a very distinct clinical impression, not however based on actual measurements, that the thickness of the uterine wall and lower uterine segment is less than in normal uteri. This impression is partially created by the weak character of the pains so frequently seen in these cases and partially by feeling the fetal parts unusually clearly

the urine with severe urinary symptoms such as urinary frequency, burning, and tenesmus. Such symptoms are very significant if followed by improvement in the patient's condition and recession of temperature.

3. Cystoscopy establishes the diagnosis, revealing a localized area of bullous edema, from the center of which pus exudes.

4. The fistula usually heals spontaneously with recession of the mass by medical treatment or surgical intervention.

5. Gynecologic cases with a pelvic mass should have a routine investigation of the genitourinary tract, including cystoscopy, as the presence of local edema of the bladder mucosa from contiguous inflammatory mass may be a premonitory sign of perforation.

6. Three cases of rupture of a pelvic infection into the urinary bladder with a collection of 21 cases from the literature are reported.

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### THE UTERUS ARCUATUS\*

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WE MAY define uterus arcuatus as that form of bicornuate uterus in which the normal fusion of the two horns in embryonic life stopped just short of completion forming an organ which in the non-pregnant state can with difficulty be differentiated from a normal uterus but which, when pregnant, exhibits marked irregularities of contour.

The most extreme grades of bicornuate uteri are for the most part anatomic curiosities which rarely have clinical significance. If such uteri contain a pregnancy they usually abort the product of conception, or carry it through and present an indication for cesarean section at term, because of malposition or dystocia or both. In such cases repetition of pregnancy in the future is avoided by sterilization, either by hysterectomy or salpingectomy. The recognition of these extreme grades of bicornuate uterus is relatively easy from careful clinical observation, since a marked degree of deformity usually leads to signs and symptoms quite different from those of normal pregnancy.

There is, however, a much more common type of bicornuate uterus (uterus arcuatus), which frequently gives rise to obstetric complications

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tation and rise to 150 to 170 for a quarter of a minute or more and then without apparent cause slow down to 100 to 110. When labor sets in, this irregularity may become accentuated in some cases and not in others. It also may be much more noticeable in the first stage of labor than in the second; when one would expect in normal cases the heart tones to become weak, rapid, and irregular, we find that they may steady down and be normal in rate and rhythm. One of the dangers of the condition is that the heart tones may stop entirely as has happened in some of our cases early in the first stage of labor. In thin women during labor, the abnormal contour of the uterus may be clearly visible when the uterus contracts, and even in stout women it can be distinctly made out by palpation. The same is true during Braxton Hicks contractions before labor begins and in the third stage of labor. A few hours after delivery the uterus assumes a more rounded contour and the bicornuate nature cannot be so easily appreciated.

The condition must be differentiated from fibroids of the uterus, especially pregnancy in the fibroid uterus. The fibroid is usually firmer than the unsoftened side of the uterus in early pregnancy for which it may be mistaken. Usually one can detect other fibroids in the uterus besides the one which might simulate the pregnant horn. The enlargement of the uterus caused by the fibroid is usually much less symmetrical. The presumptive signs of pregnancy and the Aschheim-Zondek test are valuable in differentiation.

The soft cystic pregnant horn of the uterus may simulate an ovarian cyst and the unsoftened side of the uterus be interpreted as a non-pregnant uterus. In such a case the amenorrhea of pregnancy might be ascribed to disturbances of ovarian hormone secretion. The mistake would rarely be made by a trained examiner but might be made by a general practitioner.

*Clinical Course.*—The clinical course of labor in patients who present this abnormality of the uterus differs markedly in individual cases. It is this circumstance which makes the management of these labors difficult to outline.

The onset of labor in a small percentage of cases is premature from a few weeks to two or three months. In a somewhat larger group, however, there is a definite tendency to postmaturity, varying from a few days to a week or more. This may be due, in part at least, to the failure in many cases of the presenting part to engage normally at term. This in turn is due to the obliquely transverse presentation of the fetus and to the deficiency in development of the uterine muscle. Induction of labor is frequently necessary, and the response may be weak and unsatisfactory.

When labor starts spontaneously, the pains are often weak and irregular and a slow course of labor may be anticipated. However, in some cases apparently the resistance of the cervix is proportionately less than the decrease in contracting power of the uterine muscle and as a result the first stage of labor may terminate more rapidly than normally.

through the abdominal and uterine walls. In some cases at cesarean section, certain parts of the uterine wall especially over the cornua seemed to be unusually thin before and after opening the uterus. The same impression was gained in some cases in which it was necessary to remove the placenta manually because of an abnormal third stage. It is probable also that these uteri have abnormalities of the blood supply and these combined with the abnormal musculature may explain certain clinical observations, especially intrauterine asphyxia.

The more marked grades of bicornuate uterus frequently present abnormalities of the cervix or vagina. Patients with uterus arcuatus rarely present these deformities.

*Diagnosis.*—The diagnosis of this abnormality is usually easy when the physician is familiar with the condition. The main reason for failure in diagnosis is unfamiliarity with the clinical manifestations. Early in pregnancy, up to the third month, the above-mentioned difference in size of the two sides of the uteruses will nearly always be noticeable. That containing the growing fetus may be two to three times as large as the other. The consistency is also markedly changed, the side of the uterus containing the developing fetus will be much softer and feel more cystic. In some cases a distinct groove may be felt between the right and left sides of the uterus. If the softening is more marked in the region of one cornua, the possibility of an interstitial ectopic pregnancy is raised in the mind of the examiner. The differential diagnosis by physical examination may be impossible until symptoms of rupture appear.

Later in the pregnancy, the diagnosis is strongly suggested by the shape and position of the uterus. Not infrequently the contour of the uterus will be roughly heart shaped. It is much broader across the top and the size of the horns may be approximately equal or one may be considerably larger than the other. When the latter condition is present, the uterus assumes an oblique position in the abdomen and often a large portion of the organ will be to the right or left of the midline. The lateral edge of the uterus may extend beyond the crest of the ileum in some cases.

On palpating the fetus it will be found in many cases to be in an obliquely transverse presentation; when this is true in a primipara it is practically pathognomonic. The presenting part may be found in the right or left iliac fossa and attempts to move it over to the midline and to engage it by the Mueller impression are usually unsuccessful.

Vaginal examination reveals the presenting part to be very high and the characteristic mass of the head or breech may be absent from the inlet. In those cases in which the baby is presenting by the breech, external version is difficult or impossible after the eighth month. X-ray picture confirms the clinical findings as to the presentation and position. Cephalopelvic disproportion can be estimated. However, the shape of the uterus itself is usually not easily appreciable by study of the x-ray plate.

The heart tones show a curious irregularity. In many cases as one listens over a period of a minute or more an irregularity of rate will be clearly distinguished. It may be 120 or 130 at the beginning of auscul-

ture of the uterine scar during the first stage of labor. We removed a dead baby from the abdomen and repaired the uterus, and the patient made an uneventful recovery. We plan to do a cesarean section at term in this patient if she becomes pregnant again.

Breech presentation occurred 15 times in the 134 patients who delivered from below, or 11.2 per cent. The incidence of breech in our clinic has been 3.5 per cent. The babies in this group showed an uncorrected mortality of 13.3 per cent, whereas our general mortality in breech is 7 per cent. Manual aid was practiced in all cases as soon as the umbilicus was born. In some cases the presence of a breech which could not be turned to a cephalic presentation by external version helped us to decide upon cesarean section together with other indications. The general mortality in breech is such that I believe that it is entirely unjustified to jeopardize these babies' lives when the outlook for safe delivery from below is seriously threatened by dry labor, prolapsed cord, and inefficient uterine contractions.

TABLE I

Hospital Deliveries	7,553
Bicornuate uteri	155—3.8%
Whites	121—2.6%
Colored	34—1.2%
Duration of pregnancy	
Less than 36 weeks	18
Over 41 weeks	7
Breech	15
Transverse	6
Oblique	5

TABLE II. DELIVERY

Labor induced	25
Watson	17
Bag	8
Cesarean section	21
Destructive operation	3
Forceps	<div> <div></div> <div> <div>Mid</div> <div>Low</div> </div> </div>
Mid	3
Low	9
Post-partum hemorrhage	13
Placenta delayed	9
Manual removal	4
Average length of labor in primiparas	23.4 hr.

Transverse presentation which persisted during labor occurred 6 times and necessitated version and extraction once, embryotomy once, and cesarean section twice. The oblique type of transverse presentation rarely was persistent and as labor progressed the presenting part moved into the inlet and normal spontaneous delivery followed. There were 5 well-marked cases of this type.

Midforceps were necessary in only 3 cases and low forceps were applied 9 times. This tends to show that the greatest difficulty is in the first stage. Once the cervix is dilated and the head descends into the pelvis spontaneous delivery may be expected in the great majority of cases.

Postpartum hemorrhage in our clinic is any postpartum bleeding which equals or exceeds 500 c.c. Thirteen of the 134 cases had postpartum hemorrhage by this standard. This is double the number that occur in ordinary cases in the clinic.

Weak pains and long drawn out labors have been noted in my previous communication on this subject. The average length of labor in primiparas was 23.4 hours as compared with seventeen hours which is the time ordinarily considered normal for primiparas. Two of the cases extended 75 to 85 hours, respectively. On the other hand precipitate labors were seen quite frequently. Twenty-one out of 134 cases had labors lasting five hours or less and 7 of these labors occurred in primiparas.

The second stage also may complete itself in normal time but there is a definite tendency to primary uterine inertia or to secondary inertia due to malposition.

The heart tones in such cases are frequently abnormal in rate and rhythm. Not infrequently they are found to be from 160 to 170 before labor starts or in the first stage when pressure on the fetal head or the usual causes of fetal exhaustion during labor can be disregarded as a cause. The explanation of this finding is not easy. We have felt that it is probably best explained by assuming that the deficiency in muscular development of the uterus with corresponding abnormalities in the blood supply to the placental site, may be important factors. It is also possible that deficiencies in placentation may play a role, although positive evidence of placental pathology is not demonstrable in the majority of cases. Rarely the heart tones will suddenly stop entirely. When the baby is born in such cases we have been unable to find a satisfactory explanation after thorough post-mortem examination of the baby and gross and microscopic examination of the placenta. In some cases the placenta is long and narrow instead of the usual discoid shape, and on intrauterine palpation is found extending into both horns of the uterus. Abnormalities of the third stage of labor are not infrequent and retained placenta with manual removal is more often necessary than in normal cases. Post-partum hemorrhage has been slightly more frequent in our series.

Since 1926, we have had 7,553 deliveries at the Research and Educational Hospital, of which 155 were associated with this uterine anomaly. An analysis of the clinical course of the pregnancy and labor is interesting. It should be stated that all of our patients are charity teaching cases and all are delivered by interns and students. Only a small number of the more complicated cases are delivered by the resident. Cesarean sections and difficult forceps deliveries are done by the senior members of the staff. The patients for the most part were very carefully watched throughout labor, and interns and residents, as well as members of the attending staff check the diagnosis at various times during the pregnancy and labor. As was noted in our previous paper, the general impression received is that labor is rather long and tedious, and that many patients fail to go into labor at term. An indication that this impression is correct is afforded by the fact that it was necessary to induce labor in 25 of the 134 patients that delivered from below, or 18.6 per cent. In 8 of these it was necessary to use a Voorhees' bag after the failure of quinine and castor oil induction to furnish enough stimulus to start labor. As a corollary, it may be stated that 7 of the pregnancies definitely appeared to have progressed beyond the forty-first week. On the other hand, it will be seen that 18 out of 155 patients delivered at or before the thirty-sixth week, showing that prematurity as well as postmaturity is a complication to be expected. Twenty-one, or 13.5 per cent, of the patients were delivered by cesarean section, leaving 134 patients who were delivered vaginally.

These cesarean operations were for the most part indicated by the combination of a contracted pelvis and the arcuate uterus. The result of conservatism in the management has been so disappointing that we have become more radical in recent years. We particularly elected operative intervention in those cases in which premature rupture of the membranes complicated the problem of delivery, since a long drawn out labor frequently results in intrauterine infection which greatly increases the dangers of cesarean section if this operation becomes necessary. In one-fourth of the cases, the operation was indicated by the history of difficult labor in a previous pregnancy which was terminated by cesarean section. Premature detachment of the placenta was the indication for operation in 2 cases, and eclamptogenic toxemia in an equal number. One patient who had had a previous cesarean section had a rup-

have rest periods during the course of the first stage and food and fluids must be supplied at regular intervals to prevent exhaustion and dehydration. For the same reason it is best to conduct these labors with as little sedation as possible, first because the pains are not so intolerable, and second because the stimulation to good uterine contractions should not be dulled by sedatives. In other cases the dilatation of the cervix must be carefully watched to prevent precipitate delivery. These cases are relatively rare in primiparas as compared with the prolonged labors.

The third stage is managed conservatively if bleeding is within normal limits. Pituitrin is given after the baby is born and manual removal is resorted to after two hours of ordinary third stage management. When the placenta extends into both horns, careful separation from the uterine wall must be practiced to prevent the retention of portions of placenta or membranes that might later give rise to postpartum bleeding. Following the birth of the placenta ergotrate is given by mouth or hypodermically to maintain good uterine contractions and thus limit blood loss.

The maternal mortality of 1.9 per cent indicates that the condition is to be regarded seriously as a complication of pregnancy and labor. All of these patients died following cesarean section after a prolonged test of labor, forty-one, thirty-six and fifty-two hours, respectively. Two of them had four-plus Wassermann reactions. All had contracted pelvis. One had an associated fibroid of the uterus and the membranes had been ruptured for fifteen hours. It would seem that we may have been too conservative in these cases and have allowed the test of labor to proceed too far before resorting to cesarean section. It is significant that 2 of the 3 occurred in our first 9 cases.

TABLE III. MORTALITY STATISTICS

Maternal	3 or 1.9%
Fetal	14 or 12.2% (uncorrected)
Stillborn	12
Spontaneous delivery	5
Abortions	2
Macerated	2
Destructive	3
Born alive, died	2 or 1.4% (corrected)

Fourteen fetal deaths occurred in this series, an uncorrected mortality of 12.2 per cent. Twelve of these babies were stillborn; of these 3 died during labor, one was expelled into the abdomen and died following rupture of a previous cesarean scar, one was a 1,662 gm. syphilitic premature from a mother with eclamptogenic toxemia, the third was a 3,500 gm. baby for which no apparent cause of death could be found. Two other babies were born in poor condition and died. One was a breech, fifty-four hours in labor with extraction and forceps on the after-coming head, and the other was delivered by low forceps after a fourteen hour labor, weighed 2750 gm., was in poor condition at birth and lived twenty-eight hours. The fetal mortality of the babies born alive was 1.4 per cent.

Of the 12 stillbirths, 2 were abortions, 2 were macerated, 5 occurred in spontaneous deliveries, 1 followed forceps extraction, 1 was a craniotomy, and 1 an embryotomy.

*Management.*—The management may be summed up in the expression, watchful expectancy. As soon as the diagnosis is made in early pregnancy we begin to throw safeguards around the patient by explaining to her that abortion is somewhat more common than under normal circumstances. As a result, the earliest symptoms should be detected and appropriate treatment instituted at the first sign of threatened abortion. The patient is told to avoid undue fatigue, violent exercise and all physical strain, especially at the time of month she would be menstruating if she had not become pregnant. Those patients who present cramps or bleeding are promptly put to bed and given progesterin, one rabbit unit twice a day until symptoms have subsided and twice a week thereafter until all evidence of abnormal uterine irritability has disappeared. If there has been a history of habitual abortion, the progesterin injections are started twice a week prophylactically as soon as the diagnosis of pregnancy has been established.

As term is approached the possibility of premature labor is explained to the patient, and she is advised to enter the hospital as soon as pains start. If when this occurs the baby is nonviable or just on the border of viability, attempts are made to quiet uterine contractions by bed rest and progesterin, and the patient tided over by these means until about the thirty-fourth week at which time the progesterin is withdrawn and the patient allowed more activity.

Premature rupture of the membranes offers a problem for careful obstetric judgment. If the patient is a primipara not in labor and has a closed cervix, and a viable baby, we believe a cesarean section is indicated because of the uncertainty as to the onset of strong labor pains, the time of delivery and the possibility of intra-partum infection. If the patient is already in labor and rupture of the membranes is followed by strong pains a delay of a few hours is justifiable to determine what the character of the pains will be and how rapidly the cervix will dilate. If satisfactory progress is made in this period, labor is allowed to progress to spontaneous termination or forceps applied if necessary. If unsatisfactory progress is made, cesarean section is advised. With the rupture of the membranes the heart tones are carefully observed because of the danger of prolapsed cord which is potentially more common in this condition because of the frequency of breech and transverse presentation. If the heart tones are abnormally slow or rapid, careful rectal or vaginal examination is done to detect the presence of a prolapsed cord, and if found, appropriate treatment is instituted. Unless conditions are such that delivery can be rapidly and safely accomplished from below, we do a cesarean section.

As soon as labor is well established, we watch the heart tones carefully. If they appear to be dangerously rapid or very irregular, we terminate labor by cesarean section. If, on the contrary, the heart tones stay within normal range and labor seems to be progressing normally even if somewhat slowly, we adopt a conservative attitude and allow labor to progress to spontaneous termination if it will do so without the development of alarming symptoms on the part of the baby. Because of the uterine inertia so frequently observed the patient may have to

DR. RALPH A. REIS.—I was impressed with the first paper on this subject which Dr. Falls gave in 1924, in which he called this condition the "saddle uterus." I am of the opinion that it occurs only in primiparas, for I have found it in a first pregnancy, but not in the second or subsequent ones. I wonder whether this is a structural or functional defect. I should like to know if Dr. Falls has any idea whether this condition may be due to a fundal implantation of the placenta. I would like to ask how many of these women were followed through subsequent deliveries and whether Dr. Falls found this in such pregnancies.

DR. FALLS (closing).—As to why this should be more common in white than in negro women, of course one cannot be too dogmatic. It might be related to the fact that colored women are better developed physically, have possibly more normal hormonal secretion, and their uteri develop more nearly normally in embryonic life.

The changes in menstruation in these 155 women might be another expression of their deviation from normal. Actually we expected to find a greater number of abnormalities of this type than we have.

With regard to Dr. Reis' question, we have not analyzed our cases in that connection. We have seen the deformity in multiparous women with irregular fetal heart tones. The shorter labors in multiparas reduce the number of observations of the fetal heart tones made in a given case.

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### INDIRECT EXTERNAL HYSTEROGRAPHY\*

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THE knowledge of the normal physiology and the pathologic variations of uterine motility is the key to many problems in clinical obstetrics. Studies of uterine activity have been diligently pursued on laboratory animals and the human being by many investigators. Although laboratory results have advanced our information concerning this subject considerably, such findings are not applicable in their entirety to the human being, for there exists much variation in the reproductive mechanism of laboratory animals and the human female.

Many different methods of experimental approach have been used. Some of these are suitable only for animal investigation. The methods of studying uterine activity in the human being are direct and indirect in character. A number of mechanical devices are available for use on the abdominal wall over the uterus. These procedures record the uterine action indirectly by eliciting the movements of the abdominal wall imparted to it by uterine muscle contractions. Dodek<sup>1</sup> has described such a tambour recording instrument and has used this successfully. External methods of hysterography have the advantage of simplicity and the ease with which they can be carried out in the human being. They need not interfere with the clinical conduct of the patient. Such indirect observations, however, provide only a gross picture of uterine activity. The minute changes which must necessarily precede gross action are lost in these indirect methods of

\*Read at a meeting of the Chicago Gynecological Society, February 17, 1939.

## CONCLUSIONS

1. Pregnancy and labor in the arcuate type of bicornuate uterus is relatively of frequent occurrence.
2. While spontaneous delivery without serious complications usually occurs, there is a higher incidence of abnormalities in this group of patients than in women with normal uteri.
3. The complications of pregnancy are prematurity and postmaturity.
4. The complications of labor are prolonged first stage, breech and transverse presentation, sudden intrantrine fetal death, and retained placenta.
5. Cesarean section is more frequently indicated especially in cases when weak pains are associated with contracted pelvis, or other major complications.
6. Retained placenta and post-partum hemorrhage are slightly more common.
7. Intrauterine fetal death early in labor should be anticipated by careful observation of the heart tones and prompt resort to cesarean section in appropriate cases.

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## DISCUSSION

DR. WILLIAM C. DANFORTH.—This deviation from normal is caused by a failure of complete fusion of the Müllerian ducts at the level at which the fundus is formed. A less marked form of this abnormality is described by Kermauner which he calls uterus planifundalis. He refers to a muscular weakness which may exist in this latter form.

The signs by which the condition may be recognized have been well brought out. Emphasis upon the increased broadness of the top of the uterus in the second trimester and later is characteristic. It was easily demonstrable in a case I saw some time ago in which there was a saddle-shaped hollow between the uterine horns. In this case the horns were of approximately equal size, but one side of the uterus may be considerably larger than the other. Assuming the presence of a pelvis of normal size, and the absence of obstructing tumors, the presence of an oblique presentation in a primipara speaks strongly for this condition.

If uterus arcuatus could be observed in 3.8 per cent of a series of 7,553 cases, it is sufficiently frequent that some knowledge of the character of labor in its presence is important. It is interesting that the average length of labors in primiparas was 23.4 hours, a little longer than the average in normal women. The number of women who went into labor at thirty-six weeks or earlier is greater than would be the case in a similar number of normal gravidas. The normal incidence of breech of 3.5 per cent or thereabouts, is increased in this series of cases to 10 per cent. The transverse and oblique presentations are also greater than in a normal series.

When we look over the table of deliveries it is evident that abnormal labors are more frequent for we find 21 cesarean sections, 4 destructive operations, 13 post-partum hemorrhages, and 3 manual removals of the placenta. We may express our approval of the results so far as the fetus is concerned for a mortality of 1.4 per cent is excellent.



The fundamental electrical circuit used here has been described elsewhere by Fenning.<sup>9</sup> Its use as an external hysterograph on rats and guinea pigs was first demonstrated by Bonar and Fenning.<sup>10</sup> The schematic diagram shown in Fig. 1 illustrates the modified circuit used at the present time. Since the application to the human being is new, it was deemed advisable to prepare a preliminary report. The purpose of this report is to point out the manner in which the recordings are



Fig. 2.—A typical complex curve showing the recording of the various components produced by maternal respiration, uterine motility, and fetal movements.

recording. These changes may represent essential factors in understanding the mechanism of uterine motility.

Balloons have been placed in the uterine cavity and have been attached to recording devices. The displacement of their contents by muscular contraction provides a means of measuring uterine activity. The use of a rubber balloon introduces a foreign body within the muscular organ which may lead to mechanical excitation of the uterine myometrium. In gross interpretations of uterine motility this factor may not be important, but it may cloud more accurate observations. Moir,<sup>2</sup> Adair and Davis,<sup>3-5</sup> and others have reported extensively on this method of study, particularly during the early puerperium. During pregnancy and labor these methods provide considerable technical difficulty which decreases their feasibility. They have, however, resulted in much progress and have provided an experimental approach to the rational study of oxytocic drugs.

In vitro studies of human uterine muscle strips have been recently reported by Adair and Haugen.<sup>6</sup> These experiments do not simulate true conditions in vivo, for they demonstrate only an isolated muscle response. They have advanced our knowledge of the physiology of uterine muscle.

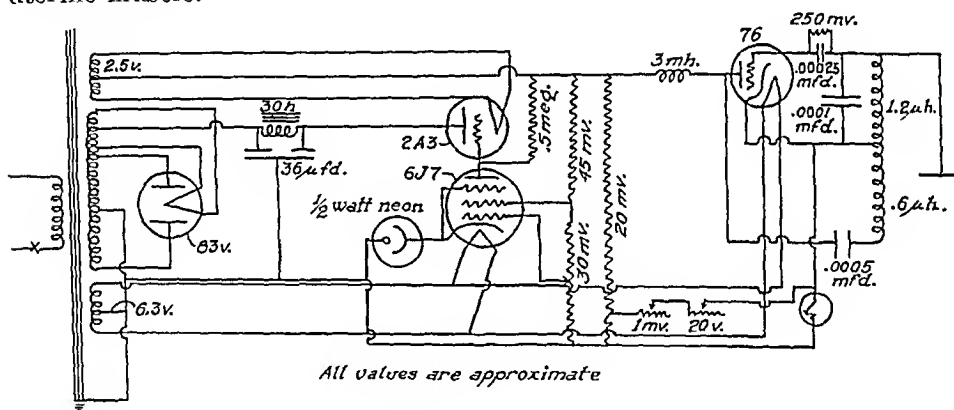


Fig. 1.—Schematic diagram of circuit.

Adair, Davis, and Parsons<sup>7</sup> in 1930 carried out a series of studies on uterine activity in women by means of an electrocardiograph. These experiments recorded action currents produced by uterine muscle contractions in a similar manner to the recording of action currents by cardiac contractions. Falks in 1935 described a similar method for use in nonpregnant individuals. He developed a special electrode that could be inserted into the uterine cavity, after which it was connected with a sensitive string galvanometer.

The method described in this paper, although indirect in character, combines the sensitivity of the electrical procedures and the ease of application of the external recording devices. By means of a specially designed electrode and a sensitive string galvanometer, it measures displacements of the uterus rather than action currents. It need not interfere with the clinical conduct of the patient so that recordings can be made throughout pregnancy, labor, and the puerperium. Graphs obtained by this method represent a true picture of uterine motility.

## THE QUALITATIVE ANALYSIS OF SIMPLE AND COMPLEX RECORDED CURVES

Any change in the position of the anterior surface of the abdominal wall with relation to the plate produces a deflection on the part of the movable member of the recorder. If the movement is toward the plate, the deflection will register in one direction on the graph, and if away from the plate, in the opposite direction. The extent of the deflection has a logarithmic relation to the actual displacement. Since the instrument has a fixed reactivity, it is possible to use the plate distance factor as a variable sensitivity control which acts to enhance or decrease the amplitude of deflection obtained with a given displacement. A greater distance of the plate from the abdominal wall allows for the recording of massive abdominal wall displacements, whereas a lesser distance permits the recording of minute abdominal wall displacements. It is apparent that the amplitude and the form of the displacement is recorded in a relatively nonlinear manner. The onset, duration, and the cessation of displacement can be ascertained in absolute time units.

Abdominal wall displacements may arise from a multitude of sources in either the pregnant or the nonpregnant woman. Each force which produces a displacement has its own characteristic form, amplitude, and duration. The forces may act singly, in sequence, or simultaneously. The actual displacement present at any one time represents the resultant of all forces acting to displace the abdominal wall toward or away from the plate electrode. The possible component factors which influence the response are:

## I. Maternal origin:

1. Voluntary movements associated with the muscular and skeletal system.
2. Respiration and its modifications.
3. Uterine activity.
4. Gastrointestinal activity.
5. Transmitted arterial and venous pulsations.

## II. Fetal origin:

1. Gross movements of the body and limbs of the fetus.
2. All other activities of the fetus capable of producing displacement of the abdominal wall, intrauterine fetal respiratory movements, fetal heart beat, and fetal hiccups, etc.

With a plate-abdominal wall separation capable of recording minute changes, any or all of the above components may produce a particular resultant curve. Such a curve is characterized by the fact that it is a pattern of many potentially possible curves. On the other hand, it is known that the various displacement components associated with the foregoing factors vary in amplitude. Hence, with an appropriate plate-abdominal wall separation, only the forces providing moderate

made, the qualitative analysis of simple and complex curves obtained by this method, and the presentation of typical recordings made during certain phases of pregnancy.

#### METHOD

Recording is accomplished by placing the fixed plate in proper relationship to the abdomen of the patient in the supine position. The plate is rigidly supported by a stand equipped with a micrometer control which allows the alignment and adjustment of the plate. The plate measures 5 by 11 cm. and is placed 2 to 6 cm. from the abdominal wall over the fundal region of the uterus. The exact distance depends upon the maximum anterior displacement during contractions. This is

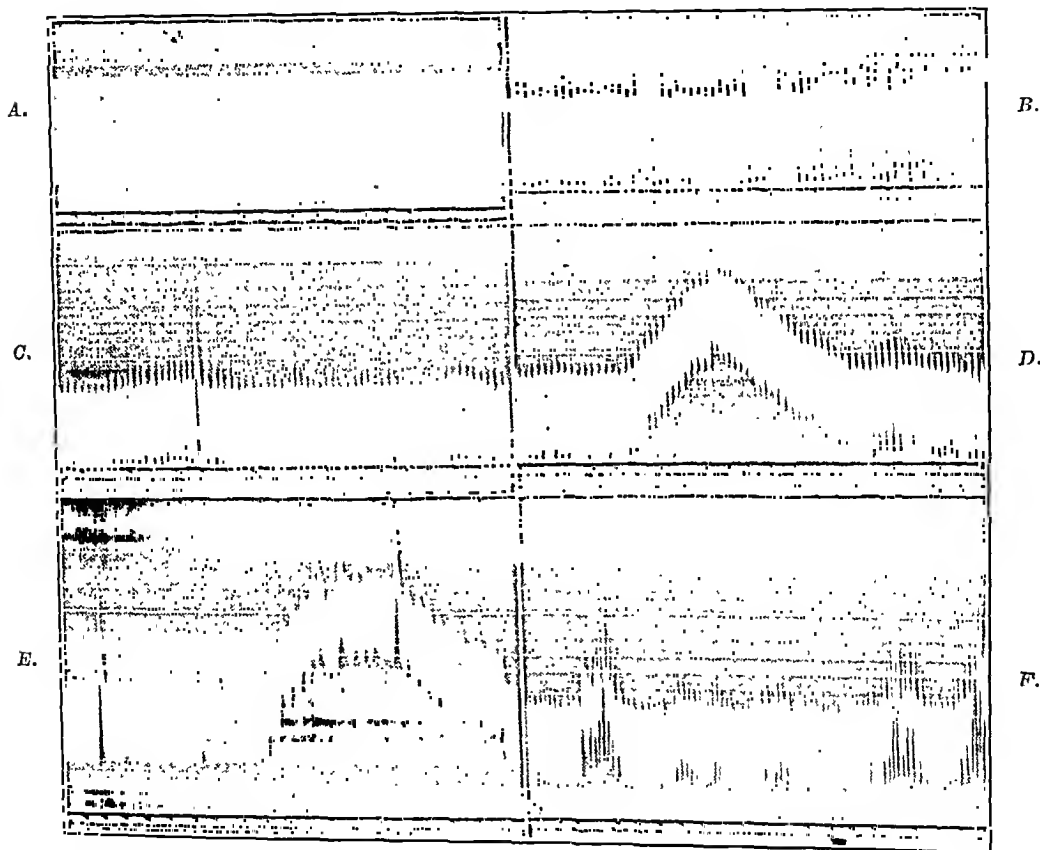


Fig. 2, A.—Blank test.

Fig. 2, B.—Maternal respiration. Mrs. H. (200637), aged 29 years, para 0, gravida i, 28 weeks' gestation, dead fetus.

Fig. 2, C.—Maternal respiration + sigh. Mrs. G. (198693), 39 weeks' gestation, live fetus.

Fig. 2, D.—Maternal respiration + uterine contraction. Mrs. H., aged 29 years, para 0, gravida i, 39 weeks' gestation, dead fetus.

Fig. 2, E.—Uterine activity, maternal respiration and sighs. Mrs. K. (188834), aged 23 years, para 0, gravida ii, post partum seven hours, packed uterus.

Fig. 2, F.—Maternal respiration, fetal activity. Mrs. W. (124570), aged 32 years, para ii, gravida iii, 39 weeks' gestation, live fetus.

determined by making preliminary observations to ascertain the extent of abdominal displacement to and from the plate. The plate distance is then adjusted to allow 0.5 cm. clearance over and above this movement. Usually a total distance of 2.5 cm. is satisfactory.

Fig. 2 represents a complex curve secured with a plate-abdominal wall spacing sufficient to allow for adequate recording of components produced by respiration, uterine activity, and fetal movements. The curve has certain definite characteristics which allow for relative analysis without the use of complex mathematical calculations. To clarify the complex curve, it was necessary to make specific recordings in which one or more typical recognizable components were present. In each case attention is called to similar appearing components present in the complex curve.

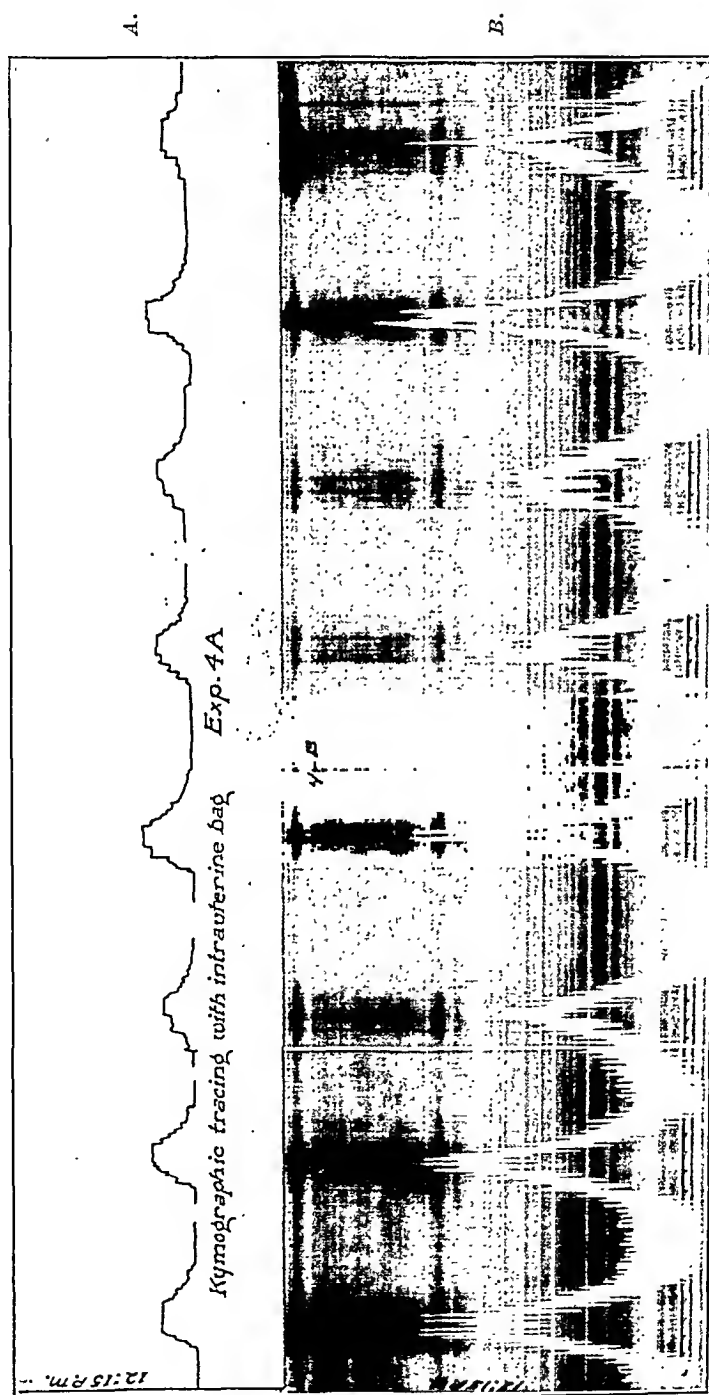


Fig. 4, A and B.—Simultaneous recording of uterine activity at the fortieth week of gestation.

or strong displacements are of any consequence. Of the above, uterine activity, respiratory movements, and gross fetal movements ordinarily provide components. This is true only when complete cooperation is secured from the patient to eliminate voluntary movements of the body.

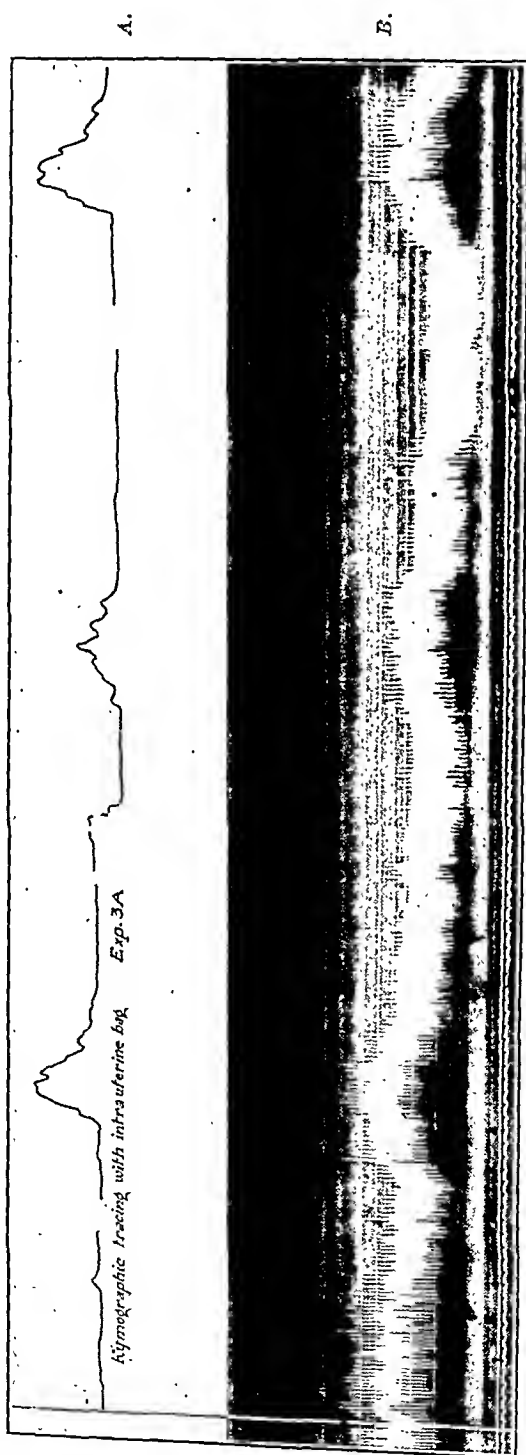


Fig. 3. A and B.—Simultaneous recordings of uterine activity on the sixth post-partum day. Mrs. S. A., para ii.

In order to provide positive proof that the slower component illustrated in Fig. 2, *D* is the result of the contracting uterus, simultaneous recordings with an intrauterine rubber balloon were made. These simultaneous recordings correlate the direct and the indirect approach.

Fig. 3. This figure shows the simultaneous recording of uterine activity on the sixth post-partum day. Curve in Fig. 3, *A* was obtained by means of an intrauterine bag and curve in Fig. 3, *B* was obtained by the method described in this paper.

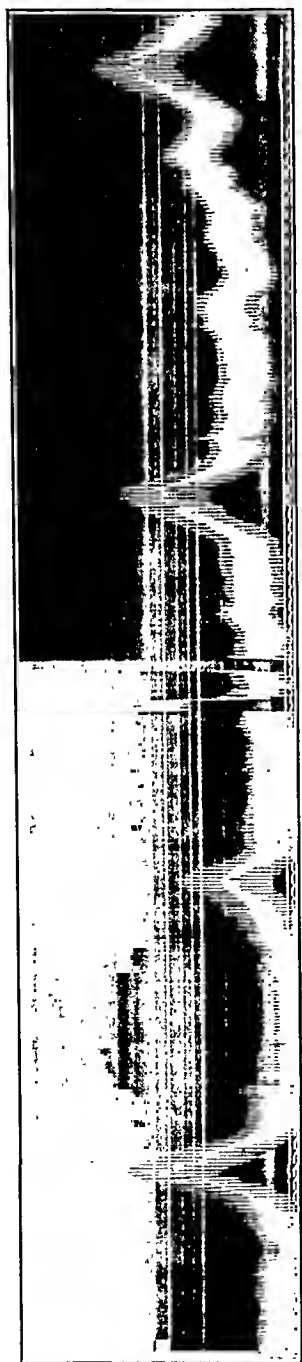


Fig. 5, *D*.—A record of uterine contractions obtained early in the first stage of labor.



Fig. 5, *E*.—Painful uterine contractions, pain signalled. Mrs. G. First stage of labor.

Fig. 2, A. This curve shows a portion of a blank test. This shows the width of the stationary string shadow and the presence of a slow unidirectional drift amounting to 1 cm. per hour. The time recording device indicates ten-second intervals.

Fig. 2, B. This is a characteristic curve in which maternal respiration provides the principal deflection component. The upstroke is an indication of inspiration while the down stroke represents expiration. The curve provides indirect evidence of maternal respiratory activity. During inspiration the contraction of the diaphragm displaces the abdominal contents, which in turn displace the abdominal wall toward the plate. During expiration the recession of the abdominal wall to its approximate former resting position produces the reverse movement of the recording member. Respiration in this case is regular and has a frequency of twenty-one cycles per minute.

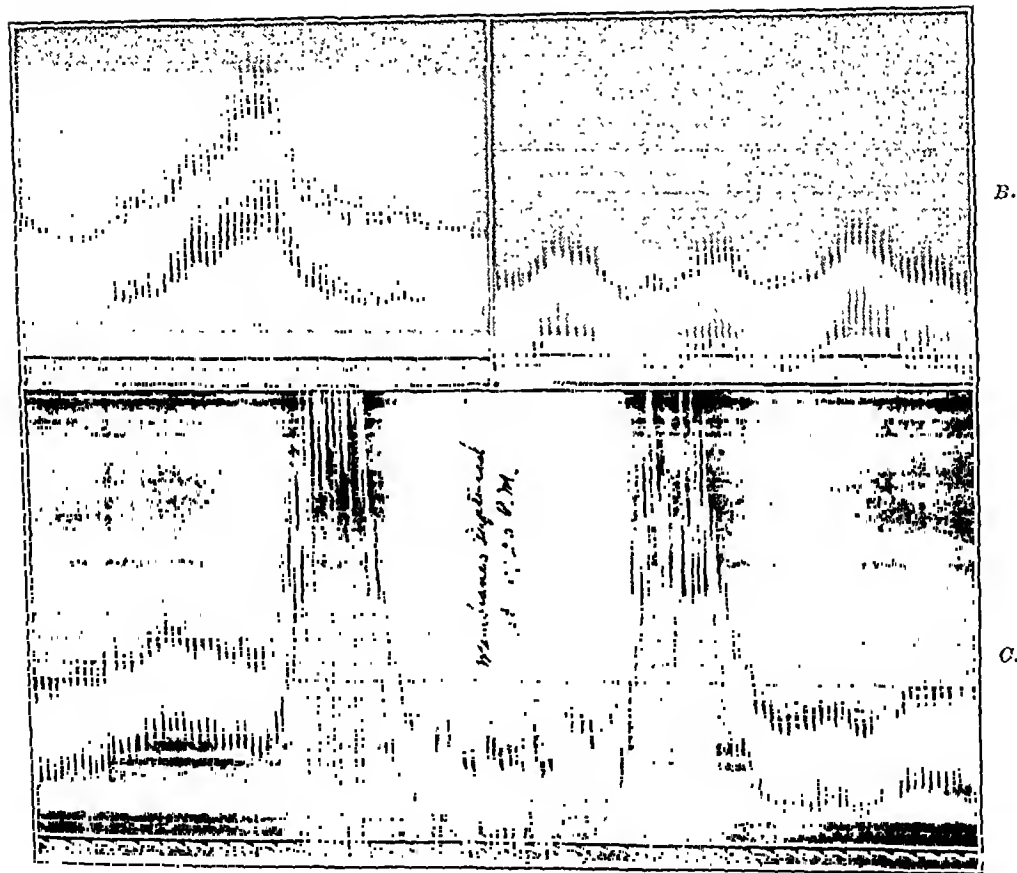


Fig. 5, A.—Painless uterine contraction (Braxton Hicks). Mrs. G. (198693), 39 weeks' gestation, five days before delivery.

Fig. 5, B.—Painless uterine contractions. Mrs. B., aged 23 years, para 0, gravida 1, twenty-five days before delivery.

Fig. 5, C.—Painful uterine contractions and modified maternal respiration. Mrs. P. (188372), aged 18 years, para 0, gravida 1, second stage of labor.

Fig. 2, C. The curve is somewhat similar to Fig. 2, B and differs only by the addition of a sigh or a natural deep inspiration.

Fig. 2, D. This curve illustrates the resultant displacement of the abdominal wall produced by maternal respiratory activity and a slower component resulting from painless uterine contraction. Attention is called to the fact that the respiratory movements show no change in frequency.

Fig. 2, E. This figure illustrates a typical graph in which the principal components are maternal respiration, sighs, and uterine contractions.



TABLE I. TEMPORAL ANALYSIS OF BRAXTON HICKS CONTRACTIONS

DURATION TOTAL	DURATION OF CON- TRACTION	DURATION OF RE- LAXATION
130 seconds	25 seconds	105 seconds
110	45	65
170	55	115
160	85	75
110	55	55
110	55	55
120	60	60
180	55	125
165	80	85
130	70	60
140	75	65
80	30	50
90	45	45
150	55	95
90	30	60
180	50	130
75	35	35
100	45	55
220	180	40
100	40	60
140	90	50
120	60	60
145	40	105
115	45	70
95	50	45
95	50	45
160	40	120
128+ (Average)	60+ (Average)	68+ (Average)

sents the temporal analysis of 27 such curves obtained from patients observed from one to ninety days before labor.

Fig. 5, *B*. This illustrates another type of uterine activity frequently observed in the ante-partum period. Similar activity has been observed in the first stage of labor. The regular, rhythmic muscle action is generally of less amplitude and duration than the changes observed in Fig. 5, *A*.

Fig. 5, *C*. This graph was obtained from a patient during the second stage of labor. It is apparent that the respiration is modified by reflex and voluntary factors. The presence of the irregular rhythm, the slowing of the pulse rate, and the held inspirations are of significance. In addition to the modified respiration during the contraction, an alteration occurs between the contractions. This is due to conversation on the part of the patient concerning rupture of the membranes during the previous contraction.

Fig. 5, *D*. This is a record of uterine contractions very early in the onset of the first stage of labor. The patient signalled the onset, duration, and cessation of pain by means of a separate control. This record illustrates an apparent contraction threshold for pain, apparently related to the intensity of uterine contraction and intrauterine pressure. Contractions 2 and 3 were of subthreshold value and were not signalled by the patient as painful.

Fig. 5, *E*. This graph was secured from the same patient one hour and fifty minutes after Fig. 5, *D*. All contractions were accompanied by mild pain. During the first stage of labor, pain is not synchronous with the onset of the contraction. A latent period of approximately forty seconds is present between the onset of the contraction and the development of pain. The pain ceases approximately forty seconds before the termination of the contraction. Additional observations indicate that as labor progresses ordinarily the latent period decreases progressively and may occupy a period of less than one second.

Fig. 4. These curves represent the simultaneous recordings of uterine activity at the fortieth week of gestation. A small rubber balloon was introduced into the uterus for the induction of labor. Four minims of pituitrin were given fifty minutes before the onset of the recording. Fig. 4, *A* represents the graph of the direct approach while Fig. 4, *B* represents the graph obtained by the indirect method.

*Typical Recordings of Normal Uterine Activity Ante Partum, During Parturition, and Post Partum.*—Fig. 5, *A*. This is a typical curve of uterine activity in the ante-partum period, designated clinically as Braxton Hicks contractions. Table I repre-



Fig. 5, *F*.—Uterine contractions in false labor.



Fig. 5, *G*.—A graph obtained three hours after expulsion of the placenta.

a double record is to find out whether or not the uterus manifests polarity, or whether the contraction starts at the fundus and proceeds toward the cervix, as it does in the dog and the monkey.

DR. M. EDWARD DAVIS.—The study of human uterine motility does not represent the simple process of recording the muscular action of the uterus. There are a number of factors which normally influence uterine motility. In the first place, there is the natural contractility of smooth muscle. Like all muscular organs the uterus undergoes periodic contractions which become grossly altered under changed conditions. Uterine activity is under hormonal control. Thus, in the nonpregnant individual, estrogenic and progestational hormones produce a varied uterine action which fits in with cyclical events. In pregnancy these hormones play an even more important role. Snyder was able to produce prolongation of gestation in the rabbit by the induction of a new set of corpora lutea in late pregnancy. Koff and Davis prolonged gestation by administering progesterin to pregnant animals. These experimental procedures indicate how profoundly hormones control uterine action. Estrogenic substances probably increase uterine motility whereas the progestational hormone decreases uterine sensitivity. The normal reproductive process requires a proper balance of these two synergistic actions.

Metabolic factors must influence uterine action. Ivy and Danforth recently published experimental studies in which it was demonstrated that calcium plays an important role in uterine tone and motility. In the presence of an increased amount of available calcium, oxytocic drugs become more efficacious in their pharmacologic action, whereas they have little effect in the absence of sufficient calcium.

The uterus is under nervous control so that nervous stimuli should and do affect uterine action. The increasing interest in the endocrine control of the reproductive organs has relegated the nervous control to the background, but it cannot be totally ignored. Last, mechanical factors may influence uterine action. Muscle inherently reacts to physical stimuli of various types. In late pregnancy, minimal stimuli may provoke such a marked response that parturition is initiated.

It is important to regard labor as a phase of a long physiologic process which begins at the onset of pregnancy, reaches its climax with the onset of labor but continues on through the puerperium. The endocrines of pregnancy prepare the uterus for receptive stimuli at or near term. Just what initiates labor is still a matter for conjecture, but it can no longer be regarded as an isolated cataclysmic event unrelated to the entire process of parturition. To understand the nature of this important episode will require careful studies throughout the preparatory stage of pregnancy. Here we may obtain a clue as to what actually starts the process of labor and controls its character.

The method which we have presented in this paper offers an excellent approach to long-continued studies of uterine motility. The sensitivity of the method allows for the study of minute changes which precede or influence more gross changes. The method does not interfere with the normal conduct of pregnancy and labor, thereby making possible long-continued observations on the same patient. Such studies should throw light on the physiology of uterine activity.

DR. EDMUND JACOBSON.—Perhaps I can explain substantially how these records are secured, what their essential features are, and how the apparatus may be developed for physiologic purposes. The essential feature of the device is this plate. You are all familiar with the condenser, as used in a radio, which commonly consists of two plates set fairly close together. The intensity in each plate of the condenser, when other things are kept constant, always depends upon

Fig. 5, F. This graph was obtained from a patient in false labor. This graph is characteristic of this phenomenon. The contractions were accompanied by pain, thereby differing from the painless Braxton Hicks contractions of late pregnancy.

Fig. 5, G. This graph was made three hours after the expulsion of the placenta. During the expulsion the uterus underwent rhythmic contractions which had a frequency comparable to the second stage of labor. Thereafter the activity decreased progressively in frequency and in amplitude; at the same time the organ decreased in size. At the end of twelve hours, the uterus may show but one contraction per hour. In order to obtain normal recordings, it is essential that natural delivery of the fetus and placenta take place. Simple manual expression of the placenta is sufficient to alter the normal course of events.

#### SUMMARY AND CONCLUSIONS

A method is presented by which uterine displacements can be recorded. This method is highly sensitive, is not dependent upon mechanical contact and in no manner interferes with normal uterine activity or with the clinical conduct of the case.

Graphic recordings are presented of typical uterine motility previously known but inadequately recorded.

Potentially the method has considerable promise as a means of making studies previously found impossible.

The apparatus at present is not electrically or mechanically perfect.

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#### DISCUSSION

DR. A. C. IVY.—I have no doubt that very good mechanical records can be made of the movements of the uterus, if one is a good mechanic. Dr. Fenning has provided us with an electrical method, and I suspect if one is a good electrician he can get good records with the method. I am familiar with Dr. Fenning's device for pulse pressure, and I think it should be applicable for making records of the exact duration of the contractions of the uterus.

The records of pain are very much like the records of pain which occur with hunger contractions in the stomach. When the stomach contracts, the individual does not record pain until after the contraction is well on its way, as in uterine contractions. Usually the pain disappears before the contraction is completed. Occasionally the pain will continue after the relaxation period is completed.

I hope before Adair and Davis complete their work that they will make a record of the movements of the uterus from the abdomen, and simultaneously make a record with a balloon in the lower part of the uterus. The record from the abdomen should give us information of the time of onset of the contraction at the top of the uterus and the bag in the lower segment should give us the time of onset of the contraction there. The point I have in mind in making such

# PROLAPSE OF THE UTERUS, HYDRONEPHROSIS, HYPERTENSION\*

## A PROBABLE SEQUENCE OF EVENTS

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### INTRODUCTION

IN A RECENT study<sup>22</sup> of 600 hypertensive vascular patients with regard to potential etiologic factors for the increase in blood pressure, 7 patients were discovered who had long-standing prolapse of the uterus with obstruction of the lower urinary tract. Although the incidence of procidentia was only 1.16 per cent, it seemed desirable to study further this type of gynecologic patient. In limiting this study to a specific type of obstructive lesion, we hoped to clarify the relationship between the urinary tract and hypertension.†

### LITERATURE

An extensive review of the literature revealed no reports directly associating hypertension and prolapse of the uterus. In 1911, Hirokawa,<sup>17</sup> however, reported the autopsy findings of an eight-month-old infant with prolapse of the bladder, slight broadening of the ureters, and enlargement of the heart with normal valvular structures. Brettauer and Rubin<sup>4</sup> (1923) reported 11 cases of prolapse in which the blood pressures are recorded in 7. High blood pressure may be considered to be present in 4 of these. Hines and Piper<sup>15</sup> (1937) reported identical twins with prolapse and hypertension. They ascribed the hypertension to a hereditary factor as the mother was hypertensive. Unfortunately a genitourinary survey was not reported.

There are numerous studies which point out various types of urologic defects as a result of prolapse. Froriep<sup>11</sup> (1824) and Virchow<sup>27</sup> (1847) reported damaged urinary tracts resulting from prolapse. Halban and Tandler<sup>14</sup> in 1907 made a very extensive study of the anatomic relationship of the bladder and ureters involved in prolapse. They showed that the bladder was pulled down with the prolapsed uterus, frequently bringing the ureters with it. The herniation under such circumstances brought about pressure and bilateral dilatation of the ureters. Mirabeau<sup>24</sup> (1908) reported 3 cases of ureteral prolapse with hydronephrosis.

Later studies by Brakemann<sup>3</sup> (1928), Schmitz and Laibe<sup>26</sup> (1929), Frank<sup>9</sup> (1931, 1938), Graves, Kickham and Nathanson<sup>13</sup> (1936), Edwards<sup>7</sup> (1937), and Danforth<sup>6</sup> (1938) generously confirm the early reports of Halban and Tandler that prolapse of the uterus is associated frequently with dilatation of the ureters and hydronephrosis.

### MATERIAL

The 15 cases comprising this study include patients encountered: in private cardiac practice, from the gynecologic service of Dr. Arthur

\*Read in part (by invitation) before the Chicago Gynecological Society, April 21, 1939.

†In conformity with others<sup>25</sup> we have used a systolic reading of 140 mm. of mercury as the dividing line between normal and high blood pressure.

the distance between the two plates. The second plate in this procedure is the abdominal wall itself, which, when it moves, alters the intensity in the plate shown in the figure. This alteration thereupon affects the rest of the circuit in such a way as to produce the recording with the galvanometer.

Therefore, by this device, uterine contractions are not recorded directly nor is anything recorded that goes on in the fetus. The record represents simply movements of the abdominal wall toward or away from the plate. These movements result partly from the uterine contractions, from the respirations and heartbeats of the mother, and from shifts of the fetus.

Obviously, these records are not to be confused with electrocardiograms, which show differences of potential in parts of the body accompanying the heartbeat; nor should it be confused with any method of recording the action potentials of uterine or other muscle. Clear recognition of these points will prevent errors of interpretation from a physiologic and gynecologic standpoint.

If desired, this apparatus could possibly be rendered more sensitive after a little experimentation. Instead of recording directly with the skin under the plate, if you place a second metallic plate on the abdomen, properly insulated but about the size of the one in the apparatus, and if you will furnish that plate with a little bias by means of C batteries, as used in radio, you can perhaps develop an apparatus which will prove much more sensitive.

DR. ADAIR (closing).—We are particularly anxious to find some method which will enable us to study uterine contractions without having to introduce any factor which in itself might modify them. This procedure does not introduce any foreign factor into the study as there is no contact with the patient.

I tried to make it clear that the recordings represent solely the reaction of the apparatus to the distance between the abdominal wall and the plate. Any factor that makes the abdominal wall move farther away or closer to the plate affects the curve. Consequently we will have to eliminate as far as possible anything that interferes with the movement of the patient, which will require complete cooperation on the part of the patient. We have also to establish a definite pattern of the different movements of the abdominal wall. I tried to show on the graphs how it was possible to pick out the respiratory movements and to differentiate the various types of movements of the abdominal wall from those produced by uterine contractions.

We are not trying to draw any very sweeping conclusions from our work. We simply offer this as a little study of a method which we think may have possibilities. Dr. Fenning is still working on the apparatus in an attempt to perfect it and determine if it has practical use.

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Restoration to normal and preservation rather than destruction of pelvic organs in gynecologic operating is emphasized throughout the article. The psychologic and physical importance of such conservation is forcibly brought out. The abuses of hysterectomies, the performance of total hysterectomy where there is a clean cervix, and the removal of the uterus where a myomectomy would suffice are all criticized. Subtotal hysterectomy is recommended as the treatment of choice over irradiation in cases of severe menorrhagia in young women where curettage and endocrine therapy have failed, since it conserves ovarian function; however, utriculoplasty to reduce the amount of endometrial tissue and abdominal curettage are two measures which it is suggested be tried first.

Conservation of ovarian tissue to the extent of enucleation of innocent simple serous cysts and dermoids is advocated. Tubal conservation with later restoration to patency by insufflation or operation is advised whenever possible.

F. L. ADAIR AND T. G. GREASY.

The clinical details of these 15 patients are portrayed best by a description of 2 who are representative of the combination of prolapse and hypertension.

L. W. was a 37-year-old housewife. The past history revealed that she had had measles and several attacks of diphtheria, gonorrhea at 21, 9 pregnancies in two marriages. Four years before beginning attendance at the Northwestern University Clinic she noted protrusion of the uterus.

Subjectively, in 1938, she complained of frequency of urination, burning, urgency, nervousness, fatigue, backache, dyspnea, and the prolapse.



Fig. 1.



Fig. 2.

Fig. 1.—Case L. W. Showing apparently normal kidney pelvises by intravenous urograms.

Fig. 2.—Case C. K. Showing marked bilateral hydronephrosis and dilated, tortuous ureters.

Objectively, she weighed 150 pounds and was 65 inches tall. The blood pressure readings ranged between 170/110 and 128/96. The heart measured 4.0 cm. to the right, 8.5 cm. to the left of the midsternal line and the transverse diameter of the chest measured 26.0 cm. The electrocardiogram showed a mild left axis deviation with borderline evidence of myocardial damage. Urologic studies (Dr. Donald K. Hibbs) disclosed a normal trigone, 1 ounce of residual urine, small ureterocele on the right, granular urethra, pus cells from both ureters and *Staphylococcus albus* from the right ureter with partial obstruction on the right. The kidney pelvises were considered normal (Dr. E. E. Barth) (Fig. 1).

C. K., a 52-year-old widow, was admitted to the Passavant Memorial Hospital June, 1934. The family history revealed that her father died of a cerebral hemorrhage. The past history revealed that she had a full-term, forceps delivery in 1911, again in 1917, and during this latter pregnancy she noted a protrusion of the womb. For seventeen years, she was treated by conservative measures, until a few weeks before her entrance into the hospital when the prolapse suddenly became irreducible.

Subjectively, she complained of weakness, urinary frequency, incontinence, incomplete emptying of the bladder, constipation, and protrusion of the uterus which she was unable to reduce.

Objectively, the findings were only those of mild obesity, a soft systolic murmur at the apex, and massive prolapse with ulcerations and brawny edema. The prolapse was reduced under an anesthetic.

H. Curtis at the Passavant Memorial Hospital, from the service of Dr. George H. Gardner of the Northwestern University Medical School Gynecologic Clinic, from a female medical ward (64) of the Cook County Hospital.

Studies of these patients included a chronologic medical history, physical examination, and routine laboratory studies. Gynecologic examinations were made by Arthur H. Curtis and George H. Gardner. Urologic examinations were made by Donald K. Hibbs with cystoscopic examinations when possible as well as intravenous pyelograms, renal function, culture of the urine and blood studies for nitrogen retention. In the latter cases, we learned to utilize the compression effect of the prolapsed uterus for the intravenous pyelograms with better results than the conventional abdominal pressure. The cardiovascular studies included frequent blood pressure readings over as long a period of time as possible. Stethoscopic and percussion findings were uniformly supplemented with two meter roentgenograms and electrocardiograms. All of these patients had prolapse of the uterus present from one to twenty-one years (Table I). All of them had undergone two or more pregnancies. Other medical diagnoses are listed. The age range was from 37 to 75, averaging 55.8 years.

TABLE I. SHOWS THE AGE, DURATION OF PROLAPSE, BLOOD PRESSURE AND MEDICAL COMPLICATIONS OF 15 PATIENTS WITH VARYING DEGREES OF PROLAPSE

NO.	NAME	AGE YR.	BLOOD PRESSURE MM. OF HG	DURATION OF PROLAPSE YR.	MEDICAL COMPLICATIONS
1	L. W.	37	170/110	4	None
2	M. G.	37	140/100	14	Hypothyroidism
3	H. L.	38	180/120	1	Cholelithiasis
4	A. C.	46	232/122	10	Diabetes mellitus Arteriosclerosis
5	G. L.	48	150/100	2	Cholelithiasis Obesity
6	M. K.	52	210/120	2	Secondary anemia
7	H. K.	53	160/80	4	Arteriosclerosis
8	M. R.	55	170/90	4	None
9	C. K.	56	90/60	21	Uremia, shock Bladder stones Secondary anemia
10	M. C.	62	170/90	18	Cardiac insufficiency
11	E. M.	68	200/110	21	Diabetes mellitus Angina
12	E. H.	68	190/130	20	Myxedema Arteriosclerosis
13	M. M.	69	210/110	1	Syphilis Obesity
14	H. W.	74	190/110	15	Hemiplegia Arteriosclerosis
15	A. B.	75	200/100	20	Cholelithiasis Coronary sclerosis
Average		55.8	177/104	10.5	



first 84 cases of prolapse entering the Passavant Memorial Hospital (courtesy of Dr. Arthur H. Curtis). Hypertension was found to be present in 61 of the 84 cases, or 73 per cent. The range of determinations of the hypertensive group was between 140/90 and 238/130. Actually, however, 97 patients were used in this study (excluding two duplications) and of these 74 had hypertension (76 per cent).

The age of these patients was from 36 to 76 years, and the duration of the prolapse from one year to twenty-seven years. Inasmuch as one would expect a high incidence of hypertension at these ages, it seemed desirable to compare our figures with a known standard. Riseman and Weiss<sup>25</sup> charted the frequency of hypertension in female patients entering the wards of the Boston City Hospital in five-year age groups. Utilizing this curve, we charted our series similarly, showing a definitely greater incidence (Fig. 3).

#### DISCUSSION

The recent reports of Longcope,<sup>21</sup> Butler,<sup>5</sup> Barker and Walters,<sup>1</sup> Leadbetter and Burkland,<sup>20</sup> Boyd and Lewis,<sup>2</sup> Leiter,<sup>19</sup> and Freeman and Hartley<sup>10</sup> show an increasing interest in the association of urologic disease and hypertension. The frequency of hypertension in our series of 97 patients with prolapse of the uterus and hypertension (76 per cent) would indicate strongly that the occurrence of increased blood pressure and prolapse cannot be explained solely upon a basis of coincidence. Factors commonly associated with increased blood pressure such as age, heredity and chronic nephritis were considered. Comparing our curve (Fig. 3) with that of Riseman and Weiss, to study the age element may seem presumptuous, considering the small number of our cases. At the ages of 50, 55, 65, and 70 years, however, our figures show almost twice as great a percentage of patients with hypertension. On this basis it would seem that the age factor could be excluded. With regard to the existence of chronic glomerulonephritis in these patients, the urinary findings were not characteristic of this disease, although transient albuminuria and casts were found in those patients observed over a period of years. The urologic evidence pointed to the infectious and obstructive character of the kidney lesion rather than to a true glomerulonephritis. It was impossible to obtain evidence which either proved or disproved the hereditary factor.

Specifically, we found the damage to the urinary tract to be varying degrees of hydronephrosis and hydroureters, with recurrent infection as has been reported by others. While the exact mechanism of ureteral compression does not seem to be entirely clear, obstruction is consistent with complete prolapse. Brettauer and Rubin<sup>4</sup> (1923) reviewed the various mechanisms of the production of urinary changes in cases of prolapse. They considered: (1) kinking of the urethra and stasis in a cystocele, (2) intramural stretching and stenosis of the ureters in the bladder wall, and (3) compression of the ureters over the edge of the levators forming the hernial ring of the genital prolapse. The uterine vessels may produce a constriction of the ureters (Fig. 4).

An intravenous pyelogram revealed a prolapse of the bladder and ureters with 25 or 30 calculi noted in the bladder. The ureters were dilated and tortuous, and the renal pelves showed bilateral hydronephrosis (Dr. James T. Case).

She re-entered the hospital four years later (1938) because of recurrence of the incarceration of the prolapsed uterus, which again had to be reduced under general anesthesia. She showed evidence of shock with a rapid feeble pulse and a low blood pressure ranging from 80/60 to 106/80. There was a high grade uremia; the blood urea nitrogen was 130.5 mg. per 100 c.c. of blood; the creatinine was 13.7 mg. per 100 c.c. of blood; the phthalein excretion was 20 to 30 per cent in two hours; the urine showed 4-plus albumin and usually was loaded with pus. The urine had a fixed specific gravity at 1.010. The blood counts showed a leucocytosis of 20,850 and no secondary anemia. This latter slowly developed over a three weeks' period. The blood nitrogen levels returned to normal in seven weeks.

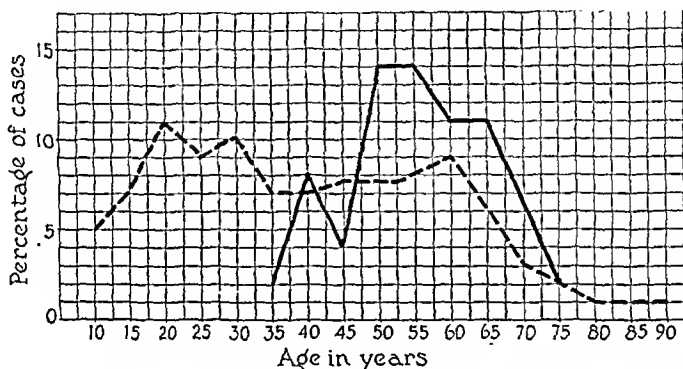


Fig. 3.—The broken line represents the percentage (ordinate) of female patients with hypertension (adapted from Riseman and Weiss). The solid line shows the percentage of hypertension in 84 patients with varying degrees of prolapse. The abscissa represents age periods in years.

This patient re-entered the hospital March, 1939 with a recurrence of the prolapse and mild uremia. The blood urea nitrogen was 33.1 mg. per 100 c.c. of blood and the creatinine was 2.78 mg. per 100 c.c. of blood. Cystoscopic examination (Dr. Donald K. Hibbs) showed gross trabeculation of the bladder. No indigocarmine dye was observed after thirty minutes. There was marked bilateral hydronephrosis and dilated, tortuous ureters (Fig. 2). The blood pressure ranged from 120/70 to 156/86. Roentgenographically, the heart measured 2.9 cm. to the right, 9.2 cm. to the left of the midsternal line, and the transverse diameter of the chest was 24.5 cm. (Dr. E. E. Barth). There was slight enlargement of the left ventricle. The electrocardiogram showed a left axis deviation.

The other 13 patients presented similar findings varying only as to detail. Gynecologically, in addition to prolapse, there were complications such as rectocele, cystocele, urethrocele and small fibroids.

Urologically, the patients presented variable roentgen findings by retrograde catheterization and intravenous urograms, from normal conditions to massive dilatation of the ureters and renal pelves. Urethral and bladder irritation were constant invariably with evidence of infection, usually *Bacillus coli* and staphylococci.

From the cardiovascular standpoint, hypertension was present consistently with varying levels in all patients (Table I) with the possible exception of the patient with the extreme uremia and shock due to the incarceration. Evidence of left ventricular enlargement was present from mild to extreme degrees as shown by the two meter roentgenograms. The electrocardiogram showed left axis deviation to be present in 10 patients and normal axis deviation in 5. Cardiac complications included congestive heart failure, coronary sclerosis and cerebral thrombosis.

An associated study of the incidence of hypertension in a somewhat larger series of patients with prolapse was made possible through the records of the

the kidney cortex. In human kidneys with hydronephrosis, reduction of the blood supply was shown by the same technique. In 1938, Egger<sup>8</sup> repeated this work with similar conclusions. It is interesting that in no instances were blood pressure readings recorded in these works; whereas Williams, Wegria and Harrison<sup>28</sup> (1938) report an increase in the blood pressure of rats with spontaneous hydronephrosis.

The role of infection also must be considered as a factor. Clinically, all of these patients presented historical evidence that they had suffered from pyelonephritis and some were under observation with that diagnosis. Pyelonephritis is given as an intrinsic cause of hydronephrosis by Mathé<sup>23</sup> (1937).

In our previous studies we have pointed out that the diagnosis of essential or hypertension of unknown origin is not justifiable unless all defects of the urinary tract, acquired or congenital, are excluded. This study, although limited to a small series of patients with a relatively uncommon type of genitourinary pathology, appears to substantiate our original contention. It would seem that a perfect mechanism exists for the production of hypertension in patients with prolapse of the uterus, when the obstruction in the urinary tract produces hydronephrosis. The enlargement of the pelvis of the kidney encroaches upon the blood supply. The partial ischemia that results produces systemic hypertension by an unexplained mechanism.

#### SUMMARY

1. In 97 cases of prolapse of the uterus, hypertension was found to be present in 74, or 76 per cent.

2. It is suggested that prolapse of the uterus with resultant ureteral obstruction and hydronephrosis causes a decrease in the renal blood supply and hypertension.

The authors wish to express their deepest appreciation to Dr. Arthur H. Curtis, Dr. George H. Gardner, Dr. Earl E. Barth and Dr. Donald K. Hibbs who made this study possible by their splendid cooperation.

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While obstruction of the ureters could be established readily with the prolapse complete, not all patients in our series could be proved as having a resultant hydronephrosis and hydroureters by present-day criteria. It had been thought that a direct relationship existed between the duration of the prolapse and the changes in the urinary tract. Statistics upon this point are fallacious, for in numerous instances previous treatment (pessaries, napkins, and surgery) had been used often with indifferent success, though often preventing complete prolapse. However, generally speaking, the patients having prolapse of short duration had minimal urologic changes demonstrable, while greater deformity was present where the procidentia existed for an extended period of time.

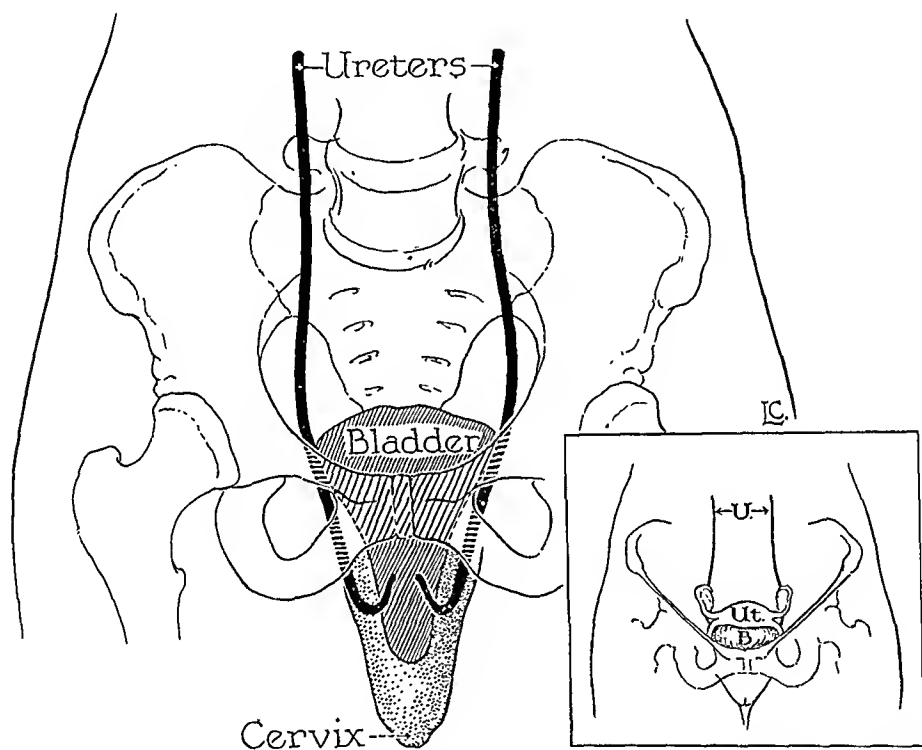


FIG. 4.—The diagram shows the schematic relationships of the ureters, uterus, bladder and bony pelvis in cases of complete prolapse. The insert shows the normal relationships.

Theoretically, it is possible for urinary obstruction, regardless of the cause, to produce hypertension. The role of obstruction in the production of hydronephrosis has been established. The significant studies of Kornitzer,<sup>18</sup> in 1922, proving a decrease in the blood supply of the kidney in hydronephrosis have not been appreciated sufficiently, and particularly so in light of the recent interest in experimental hypertension produced by obstructing the renal blood supply in animals (Goldblatt,<sup>12</sup> 1938). Similar studies include those of Hinman and Morrison<sup>16</sup> (1923, 1924) who produced hydronephrosis in rabbits, and, by using barium sulphate injections in the arterial tree, demonstrated a marked reduction in the main arterial and venous trunks of

tion of an existing hypertension. In the statistical analysis, the authors should take this into consideration, and consider parity in both the cases of prolapse and in their controls of the same ages.

DR. RALPH REIS.—This is the first attempt of which I am aware to correlate prolapse of the uterus with hydronephrosis and hypertension. Many of us who have seen many instances of prolapse of the uterus have not been aware of this relationship.

In 1928 we reported 202 patients with prolapse, many of these of long standing, and found a very low percentage of hypertension or cardiovascular disease. The second series of 220 patients ten years later showed the same thing. Hypertension occurred once in ten cases of prolapse. I am a bit fearful that if we accept the view expressed in tonight's paper too completely we will find creeping into the literature conceptions similar to the "myoma heart" of twenty or thirty years ago. These have taken many years to eradicate and are even today found in some textbooks.

I should like to ask the authors whether in relation to their study they took the opportunity of examining the eye grounds of these patients to rule out other pathology.

DR. J. D. MILLER.—I would like to ask the authors if they have studied the amount of residual urine in these patients and the relation of this to the production of hydronephrosis and other urinary tract pathology. Many of these patients are accustomed to sitting on the stool in such a way as to push the uterus up, bringing the urethra at the lower angle of the bladder so that there is less residual urine than one might expect.

DR. WOSIKA (in closing).—We hope to extend our studies to include the effect of pregnancy upon the urinary tract and hypertension. Most reports in the literature link pregnancy and hydronephrosis, and we hope to find a relation to cardiovascular disease.

That high blood pressure was found in only 10 per cent of Reis's cases seems a little startling. This is not higher than the average cases reported by Riseman and Weiss. One explanation might have been that we included only cases of complete prolapse.

Our patients showed typical eye ground findings where the hypertension was advanced. Unfortunately, we do not have complete data upon the amounts of the residual urine for the series.

We believe that the treatment of prolapse should be early and thorough to avoid the serious effects upon the urinary tract and subsequent general changes upon the cardiovascular system.

Bourne, W., and Pauly, A. J.: Thiobarbiturates in Obstetrics: Pentothal and Thioethamyl, *Canad. M. A. J.* 40: 437, 1939.

The authors have studied two sulfur derivatives of barbituric acid, pentothal and thioethamyl, with regard to their analgesic and amnesic effects in obstetrics. The degree of analgesia was fairly good following pentothal and only moderately good after thioethamyl in a group of 100 patients. Amnesia was not nearly so marked as one would wish with either drug. It should be enhanced by the use of scopolamine at the time of the first or second dose of thiobarbiturate and not after. There was no excitement from pentothal and only slight in a few instances after thioethamyl. The duration of labor is shortened with the use of either compound. No harmful effects were noted in either mother or baby, with all infants breathing spontaneously. They believe that thioethamyl deserves further study particularly concerning optimum dosage.

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6 NORTH MICHIGAN AVENUE

## DISCUSSION

DR. CHAUNCEY C. MAHER.—Our interest in this subject of hypertension and urologic pathology dates back over a number of years but this has been our first opportunity of studying a particular lesion where the obstructive mechanism was such an obvious one. Our former studies caused us to abandon the conventional viewpoint of dividing hypertension into the nephritic and nonnephritic or essential groups and led us to study the latter group with regard to mechanical defects of the urinary tract and the particular type under discussion this evening. We hoped to find some information as to the causative mechanism relating increase in blood pressure and obstruction of the urinary tract.

It would appear that in long-standing prolapse, hydronephrosis is a fairly consistent finding. Furthermore, it seems that hydronephrosis produces changes in the blood supply of the kidney. This has been shown by Goldblatt and others in animal experimentation to lead to persistent increase in blood pressure. The prolapse patients included in this study showed the usual findings of hypertensive vascular disease and the common complications. With the elevated blood pressure, there was enlargement of the left ventricle, sclerosis of the vascular tree, with congestive heart failure, coronary and cerebral thrombosis as complications.

The question should arise as to whether surgical treatment of the prolapse has produced a cure in the allied disease. To us this question is unanswered. We hope to follow as many of these patients as possible to learn whether or not the hydronephrosis is a reversible condition when the obstruction is relieved, and what effect, if any, this will have upon the blood pressure levels.

DR. W. C. DANFORTH.—I want to report a case which shows the effect of marked prolapse on the upper urinary tract. The patient was 84 years of age and had an enormous prolapse. The prolapse was reduced, and during her stay in the hospital we had some urinary studies made. On the left side we found hydroureter with hydronephrosis with two stones. On the right side was a similar hydroureter and hydronephrosis.

DR. EDWARD ALLEN.—I would like to ask if there was any study of the previous obstetric history in these patients. Hydroureter and changes in the kidney with hypertension are frequently the result of repeated pregnancies. Certainly these patients must have had repeated pregnancies to account for their prolapse.

DR. FRED L. ADAIR.—We must recognize that while the relation between prolapse and hydronephrosis and hydroureter is obvious, we cannot necessarily jump to the conclusion that hypertension is the farther result of this series of events. On the other hand, I do not see why hypertension should not result from a long-standing hydronephrosis which produces hypertension through kidney damage.

In comparing these various groups, there is a factor which should be taken into consideration. Practically all of these women who have a prolapse have obviously been previously pregnant and probably a number of times. We know that pregnancy predisposes to the development of hypertension or an aggrava-

## CASE HISTORIES

CASE 1.—Mrs. T., a 24-year-old white woman, a nurse, had been married six years without any successful pregnancies. She was rather small of stature, underweight and of the general asthenic type. Her habits had been good and her menstrual history was  $13 \times 30 \times 4$ . Blood serologic tests for syphilis were negative. Her husband suffered from acute poliomyelitis at the age of 15 and at 30 has moderate residual weakness of the left lower extremity. Careful inquiry into the family history of the patient as well as into that of her husband fails to reveal any evidence of chronic disease, abortive tendencies, or fetal anomalies. The clinical course of this woman can be studied with better perspective if it be divided into five episodes which occurred over a period of five years.



Fig. 1.—Photomicrograph of hydropic villus from "blood mole" passed by Mrs. T., Oct. 25, 1935.

I. Following a period of two and one-half months of amenorrhea, a spontaneous abortion occurred in May, 1934. There was vaginal bleeding with the passage of dark clots of blood after which normal menstruation was restored. No laboratory studies were made to confirm the diagnosis of pregnancy and the cause of the abortion was not determined.

II. A few months later amenorrhea began the second time and on Sept. 19, 1935, the patient was first seen by one of us (F. E. O'C.). She appeared to be in her sixth month of gestation with a soft symmetrical uterus whose fundus extended to within 2 cm. of the umbilicus. No fetal movements nor heart sounds could be elicited and the patient, who was extremely pale and delicate, had felt no life. She complained of weakness and anorexia and had lost weight. A Friedman test was strongly positive. Operative delivery of the products of conception was considered but further observation was thought desirable. On October 22 a dark bloody vaginal discharge began and with this a few small clots were passed. The Friedman test was still positive. Two days later Mrs. T. was admitted to the Benedictine

# RELATIONSHIP OF HYDATID MOLE TO HABITUAL ABORTION

## WITH A REPORT OF TWO CASES

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THE observation that chorionepithelioma is frequently associated with hydatidiform mole, spontaneous abortion, and in fact with any disturbance of the developing fetal trophoblast has stimulated extensive investigation of this pathologic condition about which so much still remains obscure. In the past four decades more than two thousand cases of chorionepithelioma have been reported, and it appears from these reports that the relative incidence of this most rapidly growing tumor is not as high as was formerly thought. The occurrence of this tumor following hydatid mole has been as high as 50 per cent with some observers, but the incidence in our own experience is more nearly 10 per cent, which corresponds with that of the two thousand reported cases. The fetal trophoblast no doubt develops hydatid changes more often than was previously thought and certainly many of the abortive types are not recognized. Every effort should be made, however, to determine their existence, because we know that repeated molar pregnancies may be the underlying cause for successive abortions, even if sometimes a normal pregnancy follows. Maternal mortality from mole itself may be as high as 10 per cent. The comparative ease with which the diagnosis of these pathologic changes can be made by acquainting oneself with the fairly typical clinical symptomatology, together with the use of the office procedure of aspiration biopsy, the Aschheim-Zondek and Friedman tests, should lead to more frequent recognition of these aberrant tendencies and to better judgment as to the proper care of them. Dependence on curettage alone is quite insufficient. The invasiveness of the lesion indicates that the pathologic changes may be in the myometrium. Possibly forthcoming substitutive hormonal preparations may offer a partial solution in therapy.

The following reports on two cases we have studied recently demonstrate successive abortive attempts at conception with tendencies toward hydatid changes or some other trophoblastic developmental defects. The unusual sequence of events in two individuals of the same age, similar physical development, parity and marital status is unique. The occurrence of a monstrosity and an accompanying acute hydramnios in one is the only essential difference in the clinical course of each patient. Hysterectomy was performed in both as a prophylactic measure, a procedure which we feel at the present time should be considered in other similar situations.



have been passed. No fetal elements were observed by the patient and no histologic studies were made. The menses when re-established followed a normal course until February, 1938, when the second pregnancy began.

II. It was on May 26, 1938, that Mrs. S. was referred by Dr. Eugene Galvin and at that time she was markedly dehydrated, had an albuminuria and was vomiting continuously. The fundus of the uterus was on a level with the umbilicus and seemed much larger than usual for a three months' pregnancy. The uterus was soft and boggy and the slight bleeding, which began two days previously, had become profuse. The Friedman test was positive.

Because of the patient's marked toxic state and the profuse hemorrhage, the uterus was evacuated with extreme caution. A huge quantity of material composed chiefly of grapelike masses was removed. Grossly and microscopically this was a hydatidiform mole without evidence of chorionepithelioma.

The uterus contracted promptly, no enlargement of the ovaries could be felt, and following a blood transfusion recovery was prompt. An aspiration endometrial biopsy on July 11, 1938, revealed some retained decidual tissue invading the myometrium, but the Friedman test was negative. These procedures were repeated early in September following two normal menstrual periods, and it was found that the endometrium had returned to the normal proliferative state and the Friedman test was still negative.

III. On Nov. 22, 1938, Mrs. S. was seen again at which time she gave a history of having missed two periods. A day or two before, she began to flow and to pass clots. She appeared ill. The uterus was enlarged to the size of a three months' gestation. The cervix was soft and patulous and through its canal blood was emitted. After the collection of urine on the following morning for a Friedman test, later reported positive, a curettage was performed. A practically homogeneous mass of blood clot with some placental debris in which no fetal parts were discernible was removed. Some of the villi showed hydatid alteration while others were fibrotic. Intermittent bleeding persisted for two weeks. Nausea and a feeling of exhaustion continued and the pregnancy test was still positive. The uterus was sufficiently well involuted so that thorough curettage could be done. The scrapings contained bits of myometrium invaded by Langhans' cells and scattered syncytial cell masses. These findings were suggestive of chorionepithelioma, but a definite diagnosis of this tumor could not be made. Three weeks later the pregnancy test was negative.

IV. Here again as with Case 1 it seemed that a successful pregnancy was highly improbable, and it was decided that a complete hysterectomy with preservation of the tubes and ovaries was the correct solution of this woman's problem. This operation was performed on Dec. 29, 1938. An apparently receding corpus luteum was seen on one ovary. No evidence of hydatidiform mole or chorionepithelioma could be found. A fairly large adenomyomatous infiltration was present in the wall of the uterus.

#### SUMMARY

Two very similar cases of habitual abortion are presented. The first pregnancy in each instance ended in simple abortion, the underlying pathologic changes of which were not determined. Each subsequent pregnancy resulted in either aberrant trophoblastic development or fetal anomaly. Complete hysterectomy with preservation of the adnexa was performed for prophylactic reasons on both women.

#### COMMENT

Successive molar pregnancies or those resulting repeatedly in aberrant trophoblastic development are supposedly uncommon, although Osborn in 1863 reported "uterine hydatids in four successive gestations." Lemaire observed as many as 6 in the same individual. These observations were not substantiated by histologic studies. Findley reported 31.4 per

Hospital and shortly thereafter expelled spontaneously a large homogeneous mass about 14 cm. in diameter. No part of a fetus was found in the mass nor could placental tissue be recognized grossly. The uterus was soft and boggy and there was moderate bleeding. Five hundred cubic centimeters of citrated blood was given intravenously, following which the patient reacted favorably and subsequently regained her health without significant untoward sequelae.

Nine weeks following the evacuation of the uterus a Friedman test was negative and after twelve weeks normal menstruation began. The patient had gained eight pounds, the uterus had returned to its normal size, and there was nothing suggestive of retained trophoblast in the uterus.

III. In July, 1936, Mrs. T. became pregnant for the third time. The diagnosis of pregnancy was established during the fourth month of gestation, and it proceeded normally until the eighth month when, over a period of three weeks, the abdomen became tremendously enlarged. The skin was taut over the symmetrically enlarged abdomen and signs of respiratory and circulatory embarrassment appeared. Roentgenograms showed a small fetus with an abnormal configuration of the head suggesting a malformation, a condition frequently seen with polyhydramnios. On April 1, 1937, the membranes were cautiously ruptured by making a small puncture through the fully taken up and slightly dilated cervix. The slow escape of amniotic fluid gradually brought about a decompression with only moderate maternal embarrassment. Shortly labor pains began and six hours later, under routine obstetric analgesia, a fetal monstrosity weighing three and one-half pounds was delivered. It was of a craniorachischisis type.

Subsequent aspiration biopsies of the endometrium were made at regular intervals and none revealed any pathologic changes.

IV. It was not until July, 1938, that the next pregnancy began. The Friedman test on July 25 gave a positive result. In view of the previous episodes this pregnancy caused much concern, and it was seriously questioned whether it could proceed to a successful termination with a resulting normal baby. Interference was not considered but the patient was carefully followed for evidence of abnormal trophoblastic development. During the sixth week of gestation spotting, bearing-down pains, and the usual signs of threatening abortion began. In spite of the daily administration of large doses of progestin (1 rat unit) and vitamin E (wheat germ oil m. lx) abortion occurred. The material expelled was not seen by us, but a thorough curettage was promptly done, and it yielded only endometrium showing pregnancy changes with huge tortuous glands in a stage of marked secretory activity and decidua. It would seem that the abortion was not the result of deficient corpus luteum activity. Once again a disturbance in trophoblastic development probably was the underlying cause. Six weeks later an aspiration biopsy of the endometrium yielded normal tissue and the Friedman test was negative. These findings allayed all fear that chorionepithelioma might be buried in the myometrium.

V. Mrs. T. and her husband were convinced that she was unable to carry through a pregnancy to a successful conclusion and requested some solution to the problem with which they were struggling. It was decided that complete hysterectomy with preservation of the adnexa was best adapted to her needs and this operation was performed Sept. 24, 1938. Recovery was uneventful and the patient was in good health six months later. The only pathologic change in the uterus was an extensive chronic endometritis.

CASE 2.—Mrs. S., a tall asthenic white woman, 29 years of age, had been married five years without becoming pregnant. Her health had always been good, blood serologic tests for syphilis were negative, and there was no history of her having been treated for this disease. Her husband was a normal healthy man 34 years old. No abortions had occurred during the pregnancies of the mother or either Mrs. S. or her husband.

The clinical course of this patient consisted of four distinct episodes spread over a period of five years.

I. Early in 1934 Mrs. S. became pregnant for the first time and at about the third month, spontaneous abortion occurred during which blood clots were said to

# GRANULOSA CELL NEOPLASM WITH A DISCUSSION OF POSSIBLE HISTOGENESIS\*

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THE histogenesis of granulosa cell neoplasm has been in dispute ever since Rokitansky, in 1855, provided the first example. A follicular pattern, with Call-Exner bodies, was early noted and the various designations given this tumor, such as "folliculoma," "folliculoma malignum," "adenoma of the Graafian follicles," and so on, are evidence that an origin from mature granulosa cells was considered probable. In the second decade of the twentieth century, however, the pendulum swung to a concept of derivation from granulosa cell rests. Meyer,<sup>1</sup> the chief exponent of this "rest hypothesis" based his conclusions on the following observations: (1) The proliferative activity, and probably the existence of the granulosa cell in the follicle, are dependent on the integrity of the contained ovum. (2) The number of follicles is not increased after birth. (3) Follicles suffer atresia at the time of menopause, while the peak of incidence of granulosa cell tumor occurs at a later period. (4) Granulosa cell rests are often found in the hilar regions of the ovaries of patients of all ages. Meyer's conclusions were strengthened by Te Linde,<sup>2</sup> who found a very small granulosa cell tumor in the ovarian hilus of a patient aged fifty-three years.

Interest in the "follicular hypothesis" was once more aroused by Robinson,<sup>3</sup> in 1923. This author, reporting his cases of granulosa cell tumor, observed in one definite evidence of follicular hyperplasia in the nontumorous remnant of the ovary. Recently Butterworth<sup>4</sup> made a definite contribution to the subject. Repeating some earlier work by Brambell, Parkes and Fielding,<sup>5</sup> on the effect of roentgen rays on the ovaries of mature female mice, he was able, in a number of instances, to produce tumors histologically and "functionally" identical with granulosa cell neoplasms. The primary effect of the rays was, he found, complete destruction of all ovocytes and degeneration of the follicles. In the cases in which there was evidence of development of granulosa cell neoplasm, direct origin of the tumor from residual follicular epithelium was established. Luteinization of some of these elements also was observed in a few cases, with the development of true luteomas. Butterworth's work, while not entirely nullifying the "cell-rest hypothesis" of histogenesis, lends, it would seem, considerable weight to the argument that degenerating Graafian follicles can give rise to tumors.

In a previous review<sup>6</sup> of some 400 solid ovarian tumors removed surgically at the Mayo Clinic, 30 examples of granulosa cell neoplasm were described. In none of these cases was it possible to draw conclusions relative to histogenesis. Recently in a study of papillary

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cent incidence of chorionepithelioma in his series of 500 cases of mole. On the other hand O. A. Gordon found only 21 moles out of 4,500 abortions. De Lee reported 16 cases of mole, none of which developed chorionepithelioma. We believe that careful pathologic studies will reveal a greater incidence of these occurrences than the literature indicates. Storch has already called attention to the fact that the large grossly vesicular mole is an unusual finding in molar pregnancies. With this statement we thoroughly agree. It is well known, of course, that a normal pregnancy can follow hydatidiform mole and fetal anomalies. Certainly hysterectomy should not be done because of such isolated instances; however, we feel quite strongly that this is the procedure of choice when four or more pregnancies are terminated by these pathologic processes. Not only is the risk of the development of chorionepithelioma eliminated but repeated episodes which jeopardize the physical well-being and even life of the patient are brought to an end.

If Ewing's suggestion that these pathologic processes are the result of abnormal ovarian activity is found to be true, then the time may not be far away when these tendencies can be controlled by hormonal preparations and the radical procedure herein recommended will be unnecessary.

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Baker, Ranson, and Tynen: *A New Chemical Contraceptive*, *Lancet* 2: 882, 1938.

The authors report progress in the search for an efficient chemical contraceptive. Phenyl mercuric acetate has been studied both experimentally and clinically with good results. It has a spermicidal action in  $\frac{1}{4025}$  per cent concentration in an acid and  $\frac{1}{256}$  per cent concentration in an alkaline medium. They believe it to be harmless and nonirritant as established by both experimental and clinical tests. Prepared in a gelatin base it has proved to have a greater spermicidal effect than any substance on the market and is rapidly diffused. They have also prepared it in paste form for use with the occlusive diaphragm.

In preliminary clinical tests it has proved satisfactory in their opinion. The data which are presented in this regard are inconclusive, as only 11 women using this substance only for periods of 1 to 12 months are reported. One pregnancy is reported.

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Sections of the nodule removed from the scalp revealed the picture of adenocarcinoma, Grade 2. The cells lining the alveoli were tall, columnar and had basal nuclei showing mitotic figures. Stains for mucus were positive. In no instance was there any resemblance to the picture presented by the ovarian tumor. Sections of the gall bladder disclosed the presence of typical chronic catarrhal cholecystitis.



Fig. 1.—The smooth surface of the tumor and hypertrophy of the uterus are evident.

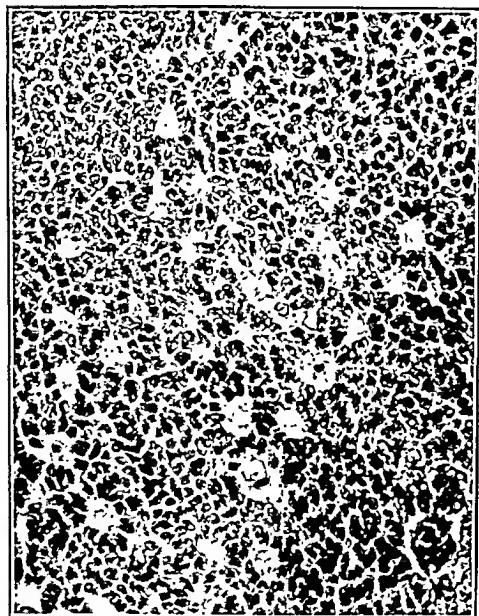


Fig. 2.

Fig. 2.—Typical granulosa cell neoplasm. Folliculoid pattern with Call-Exner bodies ( $\times 275$ ).



Fig. 3.

Fig. 3.—Cylindroid structure and large, cystic follicle ( $\times 80$ ).

Permission was obtained to perform post-mortem examination of only the thorax and abdomen and the stipulation was added that tissue of the various organs saved for study be limited to sections for microscopic examination. This circumstance made complete investigation impossible. The following data, however, were noted on gross inspection: There were multiple, discrete, subeu-

ovarian cysts,<sup>7</sup> one additional example of granulosa cell neoplasm was brought to light. It is with full realization of the dangers of trying to establish histogenetic data from a study of fully developed neoplastic processes that we are reporting this case. The occurrence of a coexisting adenocarcinoma furnishes an additional feature of interest.

#### REPORT OF A CASE

A married, white primipara, aged 53 years, was admitted to the clinic Aug. 18, 1920, because of postmenopausal bleeding. Her family history and personal history were negative. Menses had been regular and the menopause, which had occurred at the age of 47 years, was without incident. A year and a half prior to admission she had begun to have frequent vaginal spotting which had increased in severity to a profuse flow, lasting from three to ten days. These episodes of menstruallike bleeding had continued, with more or less cyclic regularity, until the time of admission. In addition to this symptom the patient gave a vague history of biliary dyspepsia, two years in duration. Urinary frequency had been present for six months. The positive physical findings were a large uterus and a mass in the cul-de-sac. Laboratory data gave essentially negative results.

Aug. 28, 1920, total hysterectomy was performed with removal of both adnexa, for a cystic tumor of the right ovary. Adhesions or metastasis were not noted at the time of operation. Sept. 9, 1920, cholecystectomy was performed for chronic cholecystitis. The pancreas appeared enlarged and the duodenum was adherent to the under surface of the liver.

The patient's condition remained satisfactory for a time but on Oct. 12, 1920, pleural effusion developed on the right side. This was aspirated Oct. 19, 1920, and 1,500 c.c. of slightly turbid fluid obtained. Drainage by catheter subsequently became necessary because of reaccumulation of fluid, but in spite of this the patient's condition remained fairly satisfactory. In November, 1920, however, subcutaneous nodules appeared at various situations over the patient's body. Dec. 20, 1920, one of these nodules, situated on the scalp, was taken for biopsy. A diagnosis of metastatic adenocarcinoma was made. Progress from this time was rapidly unfavorable and symptoms and signs of chronic intestinal obstruction developed. Death occurred Jan. 4, 1922.

The surgical material of interest in this case consisted of the uterus, both tubes, and both ovaries removed Aug. 28, 1920, and the material removed from the scalp for biopsy on Dec. 20, 1920.

*Pathologic Features.*—The uterus was about twice normal size and measured 6 by 4 by 4 cm. Both oviducts gave evidence of chronic inflammatory thickening. The left ovary was atrophic. The right ovary was entirely replaced by a cystic-solid tumor measuring 10 cm. in diameter. This tumor had a smooth, glistening grayish brown surface. On section, the tumor appeared honey-combed with cysts measuring up to 2 cm. in diameter and filled with a coagulated material. Between the cysts the substance of the tumor was brown, soft and of a homogeneously granular appearance. Fibrous tissue was small in amount (Fig. 1).

Microscopically, the endometrium was thickened and presented the picture of cystic, glandular hyperplasia so commonly associated with granulosa cell neoplasm. The left ovary and the right and left oviducts were not remarkable. The tumor of the right ovary presented the cardinal microscopic features of granulosa cell neoplasm, with a preponderance of folliculoid and cylindroid patterns. The following atypical features, however, were noted: (1) the presence of large cysts, filled with material suggesting liquor folliculi, and lined by many layers of tumor cells, but with absence of ova; (2) in certain places, notably near the periphery of the tumor, the appearance of normal follicular remnants, again without ova, presenting evidence of proliferative activity of the granulosa cells, often confined to one portion of the follicle (Figs. 2, 3, and 4).

tendency toward formation of ducts and alveoli. The carcinoma cells were of a tall, columnar type, with basal nuclei showing a moderate number of mitotic figures. A small amount of mucus was demonstrated in the tubular and alveolar spaces. Invasion of lymphatic channels by groups of malignant cells was evident in many of the sections and invasion of the adrenal vein was observed. None of the microscopic sections bore even the slightest resemblance to the picture presented by the ovarian tumor (Figs. 5 and 6).

#### COMMENT

The history, physical findings, and gross and microscopic characteristics in this case of ovarian tumor were all typical of granulosa cell neoplasm. However, the presence in these neoplasms of cysts resembling overgrown follicles is a rather unusual finding. Although it is difficult to deduce histogenic data from sections of any large tumor, it would seem, in this instance as in Robinson's case, that an origin from follicular epithelium is probable. Many follicles, appearing otherwise normal, presented localized hyperplasia of the granulosa cells with extension to involve the surrounding tissue. The absence of ova falls in line with the observations of Butterworth on the experimental production of granulosa cell tumors in mice.

In regard to the course of the disease in this case, subsequent to operation, one conclusion only seems justifiable: The metastatic nodules were not ovarian in origin. Sections taken from many parts of the ovarian tumor all presented the picture of granulosa cell neoplasm. In contrast, sections from skin, adrenal glands, lungs, heart, pancreas, and other tissues were uniformly characteristic of adenocarcinoma. To this extent only did the partial necropsy clarify the sequence of events. In retrospect, however, there come to mind the complaint of vague upper abdominal discomfort, cholelithiasis for which cholecystectomy subsequently was performed and the surgical note regarding the adhesions around the pancreas, duodenum and liver. It is known that sometimes there are few early manifestations of pancreatic carcinoma. It is known, also, that a growth in the pancreas may give rise to metastatic nodules which often overshadow the primary growth. The alveolar and tubular arrangement seen in sections of the various metastatic nodules in the case under consideration are often reproduced in metastatic carcinoma arising in the pancreas, but further than this we cannot go.

#### SUMMARY

In an unusual case of granulosa cell neoplasm, there was evidence to support the view that this tumor arises from follicular epithelium. The patient died five months after operation from carcinoma which was extraovarian in origin.

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taneous nodules measuring up to 3 cm. in diameter and situated on the scalp, dorsum of both hands, anterior aspects of the thorax and abdomen, gluteal regions and lower extremities. Nodules in the intestinal wall had caused partial obstruction of the terminal portion of the ileum, also there were nodules on that part of the peritoneum which covered the urinary bladder, in the periaortic



Fig. 4.—Portions of two hyperplastic follicles and adjacent portion of tumor ( $\times 85$ ).

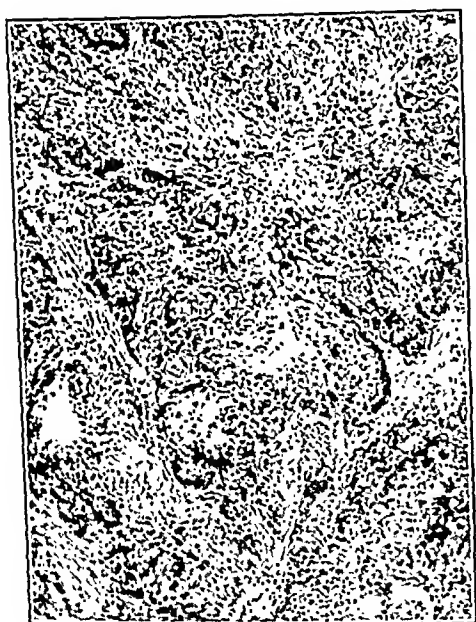


Fig. 5.

Fig. 5.—Adenocarcinoma, Grade 2, of pancreas ( $\times 100$ ).



Fig. 6.

Fig. 6.—Metastatic adenocarcinoma of skin ( $\times 250$ ).

lymph nodes and in the adrenal glands. A rather large nodule was present in the body of the pancreas, and there were other nodules in the liver. Scattered nodules were found in the lungs, on both pleurae, on the pericardium, in the myocardium, and in the mediastinal lymph nodes.

Microscopic examination of nodules from all of these various tissues revealed the same picture; namely, adenocarcinoma, Grade 2, in which there was a





Fig. 2.—Second layer, continuous mattress suture. No. 1 chromic catgut.

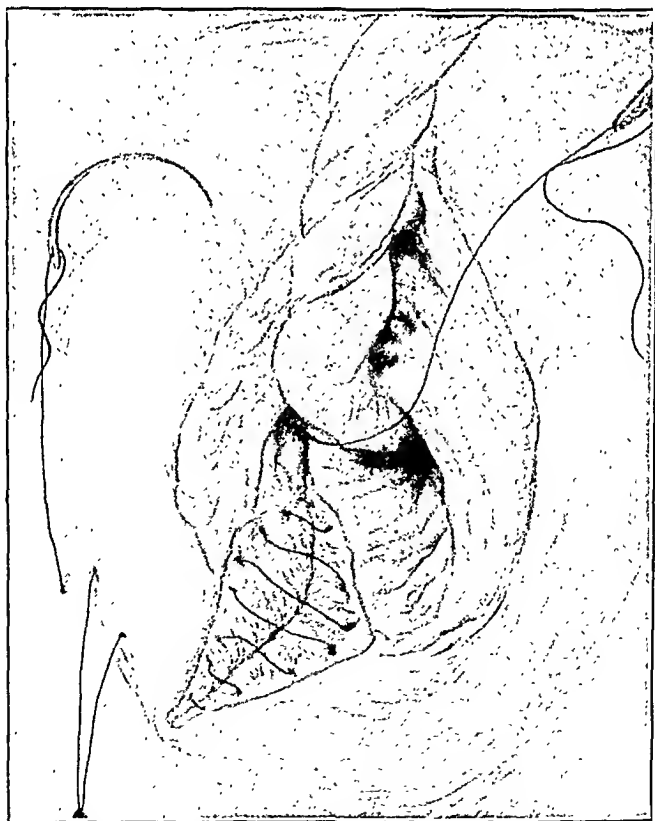


Fig. 3.—Third layer, continuous mattress suture. No. 1 chromic catgut.

## IMMEDIATE PERINEORRHAPHY WITH KNOTLESS SUTURES\*

M. PIERCE RUCKER, M.D., RICHMOND, VA.

IN JANUARY, 1937, I reviewed the history of perineorrhaphy and reported 449 repairs in which knotless sutures of chromic catgut were used.<sup>1</sup> There was one failure in this group, the lower half of one wound breaking down on the third or fourth day. A second repair with sutures of silkworm gut was done on the sixth day and this resulted in a primary union. I now wish to report upon my experience since that date.

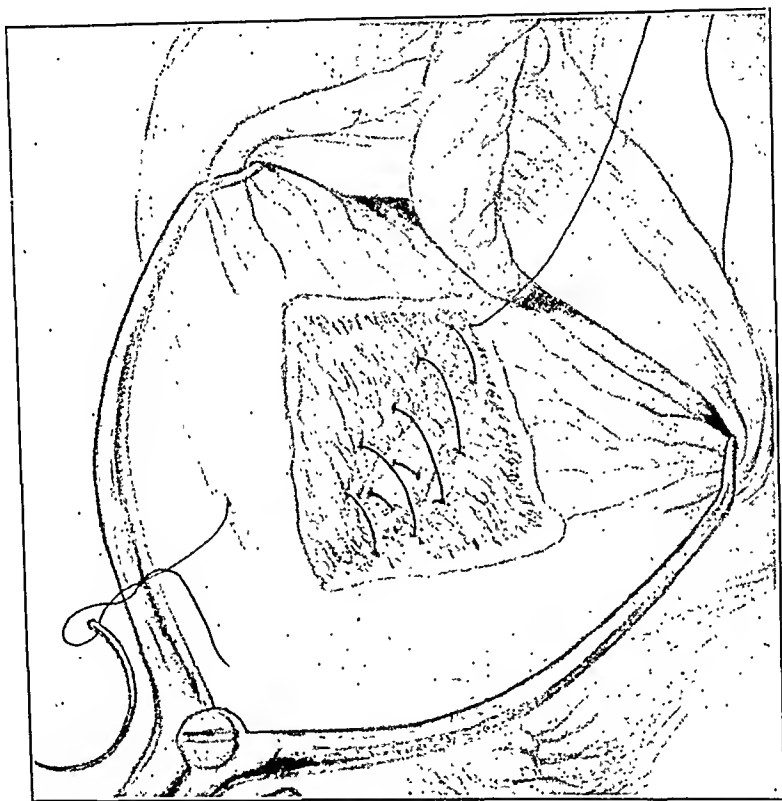


Fig. 1.—First layer, continuous suture. No. 1 chromic catgut.

There have been two minor changes in my technique. When there is free bleeding from the episiotomy wound, I use a continuous whipstitch for the deepest suture instead of the continuous mattress suture. This can be put in more quickly and controls the venous bleeding better. The second change consists of through-and-through sutures when a tear extends up the vaginal sulcus beyond the point where submucous sutures can be conveniently placed. The first suture secures both edges of the laceration as high up in the vagina as it is possible to place it. It then serves as a retraction suture and other sutures are placed one above the other until the upper angle of the wound is reached. The operation is then continued as I described in my first paper. The first row of sutures, proceeding from side to side of the wound, closes the deeper layers. When it finally reaches the lower end of the wound, it is brought out through the skin as far away from the anus as possible.

\*Read at the Greenbrier Interstate Medical and Surgical Society, April 17, 1939.

placenta. The sutures are cut flush with the skin, a solution of bichloride of mercury is poured over the vulva, a pad is applied and the patient is put back to bed.

Except when there has been a third degree laceration, the aftercare is the same as if there had been no sutures. The patient is allowed a general diet and sits up whenever she feels like it. Rarely does the patient ever mention "stitches." If the sphincter ani has been injured, the patient is kept on a liquid diet for five days. On the sixth day the patient is allowed a soft diet and is given an oil enema, if the bowels have not moved already. No further special care is given.

The present report is based upon 617 immediate repairs of the perineum. Most of them were episiotomies. Some were first and second degree lacerations. In one instance I had to deliver the placenta manually, and in doing so I damaged the repair to such an extent that I had to put in two additional rows of sutures. There was one-third degree laceration.

The evaluation of the results is based upon the condition when the patient was discharged from the hospital and upon the post-partum examination some four weeks later. Five hundred and fifty-five patients came back for a post-partum examination. Two repairs, or 0.3 per cent, broke down. The first of these was repaired with stainless steel sutures on the fifth day and a primary union resulted. The second case was that of a 28-year-old primipara who was sent into the hospital after a long tedious labor in her home. There was a constriction ring which failed to relax with adrenalin. Twenty-four hours later the patient was delivered by Braxton Hicks' version. An episiotomy was done at the first attempt. It was repaired twenty-four hours later. The wound broke down on the second day. As the patient was running a temperature of 103° F., it was thought best not to operate again. The wound healed by granulation in four weeks, leaving a broad scar, a small defect at the vulval ring, but a good thick perineum. I cite this as the worst end-result in over a thousand cases. Two patients had small patches of granulation tissue, one in the upper end of the wound and one in the lower end. In one the granulation tissue had disappeared at her second post-partum visit. I have not seen the second patient again, but when I heard from her she had no complaints.

Twenty patients had a cystocele of some degree. Ten of these had the condition before delivery and 10 developed it subsequent to delivery. This is a reflection upon the management of labor rather than on the perineal repair. Two patients had rectocele on admission. No attempt was made to correct this condition when the laceration incident to the current delivery was repaired.

Twice a strand of catgut, some three inches in length, was extruded from the anus, and was cut off. It made no difference in the end result as in both cases the union was perfect. In both patients a deep episiotomy had been done and both bled freely. In taking the deepest layer of sutures, the needle must have entered the bowel. This is easy to do and some authors recommend introducing the index finger of the left hand into the rectum to guard against such an accident. This always seemed to me a messy thing to do. From my experience with these two cases, it would seem to be an unnecessary complication of technique.

## DISCUSSION

An immediate repair of the perineum is always accompanied by considerable swelling of the tissues. If sutures are tied tightly enough to bring the edges of the wound into apposition, the next day they will be cutting and constricting the tissues. This is both painful to the patient and inimical to healing. If the sutures are tied more loosely one may not get primary union. In other words one must tie the sutures so loosely that the edges of the wound must just come in contact on the second day, a nicety of judgment I was never able to acquire. When the sutures are laid longitudinally, a good anatomic repair is secured, and if no knots are used, the sutures adjust themselves to the subsequent swelling and keep the divided tissues in apposition without constriction or interference with the blood supply. A knot in a perineal suture means pain for the patient.

I might say that the needle I use is a round curved needle with a radius of one-half an inch. This permits bringing the suture through the skin some two inches or more from the anus. A clamp is put on the suture and dropped. The weight of the clamp keeps the end of the suture out of the way. The other end of the catgut strand is then threaded on the needle and the second layer of sutures placed in a similar manner. This still further narrows the troughlike wound. This suture is brought out through the skin in the neighborhood of the first suture. The third layer of sutures is placed with one-half of a new strand of catgut. Care should be taken with this suture to bring the surface markings, such as the hymenal ring, the mucocutaneous junction, and the pigmented skin, opposite one another. The remainder of the second strand of catgut serves for the fourth layer which is a submucous, subcutaneous suture.

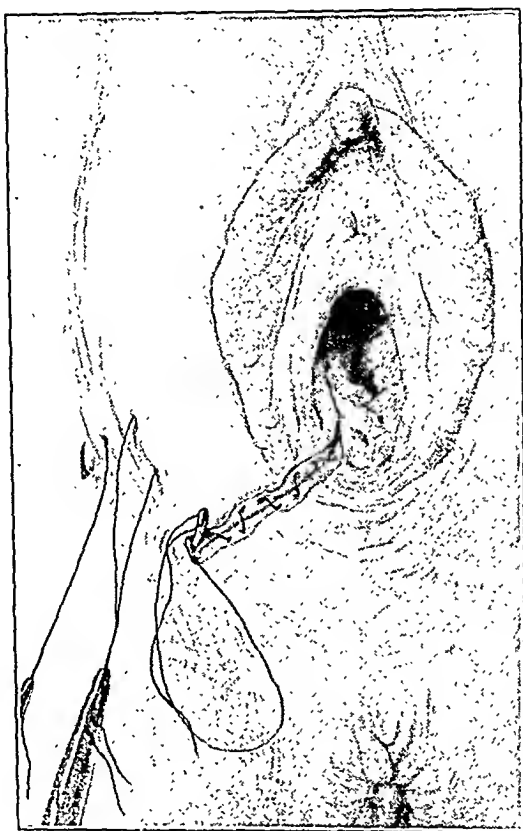


Fig. 4.—Fourth layer, continuous submucous and subcutaneous suture. No. 1 chromic catgut.

The ends of the sutures are left long until after the placenta is delivered. I prefer to operate while the placenta is separating because it shortens the anesthesia and lessens blood loss. It also removes the temptation for meddling interference in the third stage. Exceptionally the placenta separates before the operation is completed, but the uterine bleeding can be controlled by an assistant or nurse pressing on the abdomen below the uterus so as to lift it up into the upper part of the abdomen. The only serious objection to repairing the perineum in the second stage occurs in those rare cases when one has to remove the placenta manually. When this happens one has to place an additional row of stitches to restore the perineum to its former condition.

At first I thought that the expulsion of the placenta would loosen the sutures, and I would test each one to see if it could be drawn more tightly. I have never found one loosened except when I had to introduce my hand into the uterus to deliver the

Diverticula may occur in women who have not borne children. Here, trauma of coitus, congenital structural weakness, infection of the urethra must be considered as the causative factors.

The symptoms produced by urethral diverticula are directly referable to the genitourinary tract. Pain, urinary frequency, and burning are nearly always present with this condition, but involuntary loss of urine is the most annoying symptom and is quite constant. Bloody urination is an associated symptom in a few cases. A swelling noticeable to the patient is an infrequent symptom. The diagnosis of urethral diverticula is based on careful examination of the urethra and vagina. A history of urinary difficulty, associated with involuntary soiling together with the discovery of a collapsible bulge in the vagina over the urethra, leads to the suspicion of diverticulum. If urine can be expressed from the mass into the urethra after the bladder has been emptied by voiding or catheterization, the diagnosis is made even without visual intra-urethral examination. The diagnosis is absolute after direct visualization of the diverticulum opening on urethroscopic examination. The pocket may also be filled with opaque material and then examined by x-ray. Skene's abscesses are excluded by reason of their location. Solid tumors or cysts do not collapse with pressure.

The treatment of choice in this deformity is surgical removal of the diverticulum. The anterior vaginal wall is dissected free over the site of the diverticulum as in the repair of cystourethrocele. The sac can be dissected free of surrounding structures. The sac is opened so as to expose the urethral communication. That portion of the urethra with the duct and its sac are amputated. The urethra is repaired by interrupted sutures, placed so as to have a transverse urethral repair. The technique of cystourethrocele is then followed to close the vaginal defect. An indwelling catheter is left in place for a period of ten days. Electrocoagulation of the duct and sac is not advised. Suprapubic drainage is uncalled for except in complicated cases.

#### CONCLUSIONS

1. Diverticula of the female urethra are not rare.
2. Structural weakness, trauma and infection are important etiologic factors in acquired diverticula. Congenital diverticula are disputed.
3. Symptoms of urethral diverticula are referable to the genitourinary tract. Their diagnosis is simple. Corroboration is easy by urethroscopic and x-ray procedures.
4. Treatment should be surgical extirpation. Suprapubic cystotomy is usually unnecessary. Electrocautery is dangerous and may result in poor end results.

#### CASE REPORTS

CASE 1.—Mrs. M. H., white, female, aged 52 years, was admitted June 17, 1929, complaining of urgency, hematuria, and a periurethral mass for two months. Menses began at 13 years of age, regular every twenty-eight days, and lasted three days. Dysmenorrhea until first child. Menopause July, 1921. Married 33 years. Para ii, gravida iii, children 31 and 29 years of age, living and well. One spontaneous mis-

A simple method of avoiding knots has been described. The results with this method have been almost uniformly excellent. The repair broke down for a considerable extent twice in 617 cases. The final result in both cases was good. Twice there was a small superficial gaping of the wound less than a centimeter in length which was closed by a little tuft of granulation tissue, which in time disappeared.

Such a method requires practically no aftercare. If the sphincter ani is involved a liquid diet is prescribed for five days and an oil enema at the end of that time.

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MEDICAL ARTS BUILDING

## SUBURETHRAL ABSCESES, URINE POCKETS AND DIVERTICULA IN THE FEMALE URETHRA\*

WITH A REPORT OF EIGHT CASES

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**D**IVERTICULUM of the female urethra, once considered rare, is now a not unusual diagnosis after careful gynecologic or urologic examination. Over a hundred cases have been reported, and these are rapidly being added to. Many names are applied to the disorder, e.g., urethrocele, cyst, abscess, urinary pocket or pouch. However, they are not to be confused with abscesses or cysts of Skene's glands, vaginal cysts or small vaginal myomas. Urethral diverticula may be classified either as true or false. When all the layers of the urethra are involved in the process, they are called true diverticula. False diverticula are those in which only the submucosa and mucosa protrude, the muscularis having ruptured.

Hohne,<sup>1</sup> Fromme,<sup>2</sup> Jarecki,<sup>3</sup> and Johnson<sup>4</sup> believe the origin of these defects is congenital in nature. Hence, they may arise from Gartner's duct, cysts formed by faulty union of primal folds, cell rests, Wolffian ducts, or vaginal wall cysts. To support his theory, Johnson reports the occurrence of a urethral diverticulum in a newborn female child. Most authors favor the acquired theory. Diverticula, they think, are the results of injury to and infection of the urethra. According to Huddy<sup>5</sup> and Cabot and Shoemaker<sup>6</sup> there are no glands in the posterior two-thirds of the female urethra. This portion corresponds to the region in the male urethra, situated between the vesical neck and the uterus masculinus. This is a very uncommon site for outpouchings in the male. Hohne suggests that paraurethral ducts analogous to the prostate gland in the male, may open into the female urethra and later become diverticula. Furniss<sup>7</sup> thinks filling and emptying enlarge them. Ensuing infection leads to abscess formation and rupture into the urethra. This communicating opening may persist, giving origin to a diverticulum. Childbirth surely introduces serious changes into the urethra as a result of pressure, tearing, pulling, stretching, and instrumentation during delivery of the infant. Probably every urethra is damaged to a greater or lesser degree following vaginal birth.

\*Presented at a meeting of the Chicago Gynecological Society, February 17, 1939.

*Pathology.*—Specimen consisted of a previously opened cystic mass measuring 3.5 by 2.5 by 2 cm., and contained single cysts up to 15 mm., lined by a purplish gray, granular tissue. Section of cyst in periurethral region revealed a markedly thickened wall composed of dense connective tissue and bundles of smooth muscle tissue. The wall was heavily infiltrated by lymphocytes and a few polymorphonuclear leucocytes. The inner lining was composed of a thick layer of stratified squamous epithelium. Complete recovery.

CASE 5.—Mrs. S. S., aged 45 years, para i, gravida i, was admitted Oct. 7, 1938, with the following complaint: painful bearing-down feeling with dripping, with urge and marked frequency of urination and great difficulty starting for twenty-five years and especially severe during past two months. Incontinence and a mass in vagina below urethra for two months. There were also some backache and constipation.

Cystoscopy examination Oct. 10, 1938, revealed a normal bladder. A fistula was found on the posterior wall of the urethra. This appeared infected and pus would exude when pressure was exerted from within the vagina. On Oct. 14, 1938, this mass was resected through the vagina and found to be an infected diverticulum of the urethra about one-half inch from distal opening.

*Microscopic Diagnosis.*—Dense and loose fibrous tissue covered in part by non-cornifying stratified squamous epithelium. In one area deep in dense connective tissue was a portion of what was apparently a sinus tract containing pus and with chronic inflammatory reaction in its wall. No pocket lined by epithelium was noted.

CASE 6.—Mrs. M. D., aged 41 years, was admitted Aug. 28, 1938, complaining of backache, lumbar and sacral, for two years since birth of last child; coccyx fractured during delivery. She had had dysuria for three years, stress incontinence four years, and pyuria and hematuria for five to six years. A right oophorectomy and appendectomy were done in 1921. Seven years ago she received a fractured skull and a possible pelvic fracture in an accident.

She had been married twenty-two years. Para iii, gravida iii. Instrument with first labor. Pressure on a plum-sized mass attached to urethra, caused pus to exude from urethra. Cystocele and rectocele. She had an eroded cervix with retention cysts.

The diverticulum was dissected free and the duct excised. Urethra was repaired and cervix amputated. A cystourethrocele was repaired and vaginal wall closed. Patient left hospital on tenth postoperative day in good condition.

CASE 7.—Mrs. A. H., aged 48 years. Incontinence for three to four years, with dribbling and bed-wetting. Gravida i, induced abortion; para 0. In 1926, salpingectomy; 1937, vaginal plastic; 1938, operation for repair of urethrovaginal fistula.

*Examination.*—Normal female except for abdominal and vaginal scars and local pathology which consisted of essentially a bulge in the anterior vaginal mucosa just below urethra and 0.5 cm. from urethral meatus. Pressure caused urine to exude from urethral meatus. Cystoscopic examination revealed normal bladder. Urethra presented a small opening in posterior wall 0.5 inch from meatus, which communicated with the vaginal swelling.

*Diagnosis.*—Urethral diverticulum.

At the first operation an attempt was made at closure which resulted in urethrovaginal fistula, at the second operation the fistula was dissected and closed, with healing and was otherwise intact.

CASE 8.—Mrs. L. R., aged 35 years, para 0, was admitted Jan. 22, 1939. Pregnancy, sixteen years ago, terminated by induced abortion at two months. Complained of pain in vagina and had had vesicle tenesmus for five years.

Perineum and buttocks showed scars from previous fistulotomy. Vagina admitted two fingers. There was a plum-sized mass on anterior vaginal wall. Cervix, uterus, and adnexa were negative. Cystoscopic: Urethra was elongated and reddened. One-fourth inch from the internal meatus was an opening, from which pus exuded on pressure to mass in vagina.

carriage between. First delivery by forceps with second degree tear; second normal. Repair of cervix and perineum at 26 years. Curettage and radium November, 1928, for postmenopausal bleeding.

Physical examination negative except for vaginal findings. Perineum scarred; second degree cystocele. One inch from urinary meatus was a walnut-sized mass which fluctuated and, on pressure, pus escaped from the urethra. Cervix and pelvic viscera were negative. A diagnosis of periurethral abscess was made and on Feb. 18, 1929, an incision was made through the vagina to drain the mass. On Feb. 22, 1929, examination revealed the pocket again filled and a large amount of pus was pressed through the urethra. March 6, 1929, examination revealed an abscess about the size of a small marble with a sinus opening into the posterior portion of the urethra 1.5 cm. from the internal meatus. The cavity was again opened and thoroughly cauterized with the actual cautery. A retention catheter was inserted in the bladder and the urethra reconstructed around the catheter. Patient was discharged March 23, 1929. At present patient has no symptoms but the entire one-third of the urethra is missing due to the slough following the above procedures.

CASE 2.—Mrs. V. V., aged 26 years, para 0, gravida 0, married 2½ years, was admitted Feb. 11, 1933, complaining of occasional vague pains in the pelvis since marriage, never severe or constant. Her husband, a physician, examined her and diagnosed a cyst of the anterior vaginal wall.

Physical examination on admission was negative except for the bimanual findings. The vagina admitted one finger. The cervix was nulliparous. Uterus in good position, of normal size. The adnexa were negative. Speculum examination revealed an erosion of the cervix but no cyst was demonstrable. The patient was instructed to return for further study and on March 5, 1933, upon re-examination a walnut-sized, cystic mass was found on the anterior vaginal wall at about the middle third of the urethra. On further pressure the mass disappeared, clear fluid escaping through the urethra. A diagnosis of urethral diverticulum was made and on March 10, 1933, the cyst was resected. Sections of this 3 cm. cyst with a smooth internal lining and pale white fluid contents, revealed the cyst to be lined with flattened epithelium and covered on one side with stratified squamous epithelium.

CASE 3.—Mrs. C. R., aged 37 years, gravida iii, para i, two induced abortions, was admitted Nov. 29, 1937, complaining of a thick white discharge from the urethra for the past year. Patient consulted her physician who found ++++ albumin in the urine and prescribed a diet and medication. Urinary frequency and nocturia of 4 to 10 times persisted. Patient noticed that for one week before menses coughing or straining caused her to soil her clothing.

In 1922 pelvis was fractured in two places. Curettage was done eight years ago for bleeding after second abortion. Physical examination was negative. On bimanual palpation a bulging mass was found in the anterior vagina. Pressure on this mass caused pus to exude from the urethra. Pelvic examination was otherwise normal except for a multiparous cervix and a slightly relaxed perineum. Cystoscopic and urethroscopic examinations on Nov. 30, 1937, revealed a fistula of urethra in the posterior one-third. It was impossible to pass a urethral catheter into the opening but pus could be seen to exude when pressure was made in the vagina. On Dec. 10, 1937, resection of diverticulum was done.

CASE 4.—Mrs. G. W., aged twenty-six years, gravida ii, para 0, was admitted March 9, 1938, complaining of a mass in the vagina which increased and decreased in size. Patient had been under care of a physician for past two years, being treated for a cyst. Three years ago at the time of her last miscarriage she was told she had a cyst but had no symptoms and therefore did not return for treatment. During the past two years she has had a dysuria, straining and burning in nature.

Examination revealed an egg-sized mass in anterior vaginal wall. Pressure upon this mass causes pus to exude from the urethra. The introitus and vagina otherwise negative. Cervix firm and closed. Fundus in ante-position, normal size. Adnexa negative. Vagina bathed with a milky discharge. Urine examination: ++++ albumin; ++ pus and blood. Kahn: negative. March 12, 1938, operation.



## A PRACTICAL TREATMENT OF GONORRHEAL ENDOCERVICITIS

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PUERTO ARMUELLES, PANAMA, C. Z.

THE introduction, within recent years, of artificial fever therapy, pelvic short wave diathermy, the Elliott treatment, and sulfanilamide saturation, have produced a confusing period of transition in the treatment of gonorrhea in the female. The present study seeks to emphasize a modification of an older and better understood approach to this problem: cauterization or fulguration of the cervix and its subsequent treatment. I am aware that improvement in heat therapy or sulfanilamide-like compounds may already have reduced some of the objections to these recourses. A simple, practical method of treatment, which may usually be conducted in the office, is herewith presented. It has yielded gratifying results in my hands.

Because the cervix is the principal focal point of gonorrhea in the female and the only one presenting a formidable barrier to eradication of the disease, consideration of its treatment defines and limits this clinical summary.

### CAUTERIZATION OR FULGURATION OF THE CERVIX

In contrast to the generalized systemic action of fever therapy and chemotherapy is a direct attack upon the deep-seated glands harboring the gonococcus in the endocervix. The futility of topical applications in this area was recalled by Notes<sup>1</sup> who reported only 8.7 per cent cures from the use of local antiseptics, and 19.3 per cent cures following one or two cauterizations of the cervix in dispensary patients. He adds "no patient who cooperated failed of cure." Following cauterization, Notes applied silver nitrate 25 per cent solution to the cervix once a week to stimulate local reaction and promote drainage. Apparently, arrest of disease required about a year.

I advocate a modification of this method. The cervical canal is cleansed, swabbed with 5 per cent mercurochrome, and anesthetized with a 5 per cent solution of diothane and 5 per cent benzyl alcohol in 55 per cent alcohol, applied on cotton wrapped applicators. Care is exercised *not* to pass the applicator, or the cautery, beyond the resistance encountered at the internal os. Anesthesia is usually adequate in ten minutes; if it is not, the cauterization had often better be done under a general anesthetic. If the canal is narrow, it is first gently dilated. Either the Post cautery or Paquelin cautery may be used; if the former, with incisive radial strokes, for the latter with a gentler touch. A thorough cauterization of the mucosa of the endocervix should be attempted. Repetition will not often be necessary.

The patient has been instructed that following or quite independently of cauterization, she may develop a pelvic infection. She is advised to go immediately to her home, and to remain in bed for two days. Throughout the entire course of treatment, she is instructed to do no active housework, to abstain from alcohol, exercise, dancing, and coitus; fatiguing social activities, prolonged shopping tours and sustained walking or standing are also interdicted. Observance of these restrictions constitutes the best safeguard against pelvic extension, which has occurred in 20 per cent of our cases.

On the second day following cauterization, the patient reports for aftertreatment. In the dorsal position, with speculum in position, a low pressure cleansing douche of potassium permanganate, 1-2000, is given. The vagina is dried, and a small gauze sponge placed beneath the cervix. A tightly twisted cotton tipped applicator is

*Past History.*—Nov. 17, 1938, fistulectomy. At this time there was acute urinary retention. On examination a mass was found in the vagina, and catheterization relieved the condition. Kahn test was found negative. The patient was operated upon on Jan. 28, 1939.

Complete healing and freedom of symptoms have been obtained in each case.

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#### DISCUSSION

DR. EUGENE A. EDWARDS.—Eight similar cases of urethral diverticula and pocketing from our service have been reported by McNally.

There is one case that warrants description—a patient with a calculus in a true diverticulum. This woman gave a two-year history of a severe backache, later of pain in the vagina, especially marked on sitting down. There was occasional hematuria and incontinence of urine. Urethroscopic examination and x-ray showed the stone, probably a calculus in an already formed diverticulum.

Five of our patients gave a history of previous pelvic infections. Only four had had full-term pregnancies. This might indicate a relation between Skene's duct infection and periurethral abscess as a causative factor.

The diagnosis of these pathologic lesions around the urethra is not difficult. The diagnosis of seven of our cases was made by the gynecologists, but I cannot agree with Schmitz that the treatment of urethral conditions is a gynecologic problem. I feel that they belong in the field of urology.

DR. C. W. BARRETT.—I have seen a few of these cases. I have found no great difficulty in curing them by simply opening the urethrovaginal wall, dissecting out and tying off the sac. The gynecologist is in a better position to treat this lesion than the urologist, for it frequently requires some supporting operation with which the gynecologist is more familiar.

DR. J. DUANE MILLER, GRAND RAPIDS, MICH.—Occasionally when these lesions are not readily palpable, the patient may be treated for a considerable period of time for chronic urethritis without permanent relief. Under these circumstances, investigation with contrast media will often show a small diverticulum, the removal of which will result in a cure.

DR. SCHMITZ (closing).—Most of our cases were in multiparas and at least 50 per cent were due to injuries at childbirth. I think, therefore, that these injuries are out of the realm of the urologist.

I agree with Miller that after other possibilities have been investigated it is necessary to have x-ray examination with contrast medium to isolate the opening of the diverticulum.

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Speert, Harold: The Passage of Sulfanilamide through the Human Placenta, Bull. Johns Hopkins Hosp. 63: 337, 1938.

Sulfanilamide, given by mouth to pregnant, full-term women during labor, passes readily to the fetus, the concentrations of both the free and acetylated forms acquiring equilibrium between the fetal and maternal bloods within approximately five hours. The drug also passes rapidly into the amniotic fluid.

C. O. MALAND.

fulguration should be especially efficacious in dealing with a gonococcal infection. This advantage is apparently offset, however, by the added difficulty in estimating the tissue-effect of fulguration as compared to that of the electric cautery. My experience is that the results obtained are identical; in the fulguration cases there has been a slightly higher incidence of subsequent pelvic infection.

### RÉSUMÉ

1. A satisfactory method of treating gonorrheal endocervicitis consists of one- or two-stage cauterization or fulguration of the cervix followed by daily application to the cervical canal of phenol, silver nitrate solution, and formalin.

2. Adequate saturation with sulfanilamide-like compounds (neo-prontosil, uliron) may advantageously precede and follow the cauterization.

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UNITED FRUIT CO. HOSPITAL

## AN UNUSUALLY LARGE TUMOR OF THE VULVA\*

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(From the Gynecological Service of Dr. Hellman at Sydenham Hospital)

**FIBROMAS** and fibromyomas of the vulva are comparatively rare. That a tumor of the vulva should have been allowed to grow to the size of the one here described is almost incredible.

Leonard<sup>1</sup> in a report on "Fibroma and Fibromyoma of the Vulva" in 1917 noted their rarity when he stated that in 23,000 gynecologic admissions to the Johns Hopkins Hospital, there were but 6 cases of fibroma. Nearly all fibromas showed degenerative changes if they were allowed to develop for too long a time, and 22 per cent showed malignant changes (14 out of a series of 64). Vascular changes and swelling were noted at the time of menstruation and pregnancy.

The patient was a colored woman, Mrs. A. Y., aged 28 years, admitted to the Gynecological Service of Sydenham Hospital on May 2, 1938.

*History.*—In 1929, the patient noted a mass on the vulva about the size of a walnut. Urination was not interfered with nor was menstruation affected. This mass was excised in a hospital in Savannah, Ga. Six months later, while making her home in New York, she noted that the mass had reappeared. In November, 1930, she was admitted to Kings County Hospital where a biopsy was done and she was discharged with the diagnosis of papilloma of the vulva.

Since that time, the mass gradually became larger and in the six months preceding admission grew to such an enormous size that walking was impossible without supporting the tumor in a sling. Urination on admission to the hospital was only possible when the patient stood up and lifted the tumor. Defecation was not interfered with. Menstruation ceased September, 1937. No bleeding occurred from the tumor although a slight discharge was noted from the mass for several weeks preceding admission.

The patient's record showed a 4-plus Wassermann reaction at Kings County Hospital in 1930, and she received several courses of intravenous and intramuscular injections.

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dipped in pure phenol and introduced into the cervix, any surplus being carefully removed with alcohol. The gauze pad beneath the external os protects the vaginal mucosa. It is then lifted with forceps and by exerting gentle pressure used to dry the cervical canal. Treatment is carried out daily, with 25 per cent silver nitrate solution, and pure formalin used on succeeding days, in rotation with phenol.

The effect of these potent antiseptics is to induce an intense local tissue reaction in the cervix. This is characterized by marked edema, redness and abundant sero-sanguineous discharge. Gonococci extruded upon the surface of the canal by this tissue response are destroyed by the antiseptic application of the succeeding day. If exposure of the cervix presents no unusual difficulty, the treatment is attended by little, if any, pain. Interruption of daily cleansing and antiseptic application is not permitted during the menses. Increased blood flow through the affected parts during this period is thought to emphasize the indication for destruction of gonococci on the surface of the cervical canal. We have not observed a greater incidence of pelvic extension during or after the menses in individuals so treated.

Smears or cultures for gonococci are made once or twice each week. One will be disagreeably surprised to encounter the organism after weeks of treatment. Two or three successive negative reports permit cessation or reduction of office treatment.

After withdrawal of the antiseptic applications, swelling and inflammation of the cervix subside, the slough separates, and a healed, healthy canal is produced. Dilatation of the cervix, including the internal os, is now carried out with sounds. This should be repeated twice at intervals of one and two months to assure patency. It has not been found that this method of treatment induces stenosis of the canal, except in certain instances in which the infection is extremely acute at the time of the cauterization. The average time required for daily treatments has been from six to eight weeks. Cure has resulted in all cases presenting full cooperation.

#### COMPLICATIONS AND CAUSES OF FAILURE

Inadequate cauterization is the principal defect of technique. The light, radial "strokes" of the cautery used for nonspecific erosion and endocervicitis do not suffice, since the deepest glands must be exposed to ensure eradication of gonococci. Cauterization should be temporarily withheld in extremely acute infections with marked edema of the cervix and profuse discharge. Inability to secure adequate exposure of the cervix, and incomplete topical anesthesia, call for a short general anesthetic agent. Should marked bleeding occur during cauterization, the operation is best terminated at once. A dull red cautery tip may seal the bleeding point. Failing this, the cervical canal is swabbed gently with a saturated solution of potassium permanganate for hemostasis, and the vagina packed. Moccasin venom or whole ovarian extract may be injected. In the uterus undergoing fibrous involution, annoying hemorrhage is unfortunately not uncommon. In such instances, a second attempt at cauterization should not be made for a week or longer. A recurrence of hemorrhage will then force abandonment of the cautery procedure. Widespread pelvic infection following cauterization, reported by Cannell and Douglass,<sup>2</sup> has not been observed in greater degree than that of spontaneous extension of pelvic inflammatory disease occurring in untreated or conservatively managed gonorrhea. Attention must be called, however, to the possibility of bladder injury.<sup>3</sup> It is my impression that this accident cannot occur if the operator is at all times conscious of the exact position of the entire cautery blade, and its heat potentiality. The implication is that the cervical canal must be sufficiently wide to admit the cautery without "forcing." This frequently entails preliminary gentle dilatation as far as, but not beyond, the internal os. Elongation and thinning of the cervix in procidentia demand extra caution.

#### FULGURATION VS. CAUTERIZATION

If the cervix is to be fulgurated, the monopolar current should at present be selected. Appraisal of the deep tissue injury inflicted by the bipolar cutting currents is too uncertain to risk perforation of the cervix, bladder, or uterus. I have found a satisfactory instrument in the Jarosch cervical electrode with unipolar energy. Its shank prevents passage through the internal os. The greater heat penetration of

*Pathologic Report.*—(Dr. Arthur A. Eisenberg.) Gross specimen weighed 5,000 gm. (11 pounds) and measured 13 by 10 by 9 inches. Skin is coarse and has several areas of pigmentation. The tissue is firm and on section is somewhat whorled. The whorls are located around softer areas 2 by 6 cm. The entire right portion has a gray white surface, but the softer areas are pink. The left portion is succulent with a small amount of connective tissue. A large amount of fluid escapes from the cut surface; this fluid coagulates on standing.

*Histologic Report.*—There is present a pale, fibrous, collagenous tissue with an admixture of what resembles myxomatous tissue, although the latter is not at all prominent. The tissue is rather vascular with both medium and small sized vessels. The former occasionally show considerable thickening of the wall due to medial thrombosis, but the intimal changes are not prominent. There are numerous areas of edema and irregular spaces between the fibers.

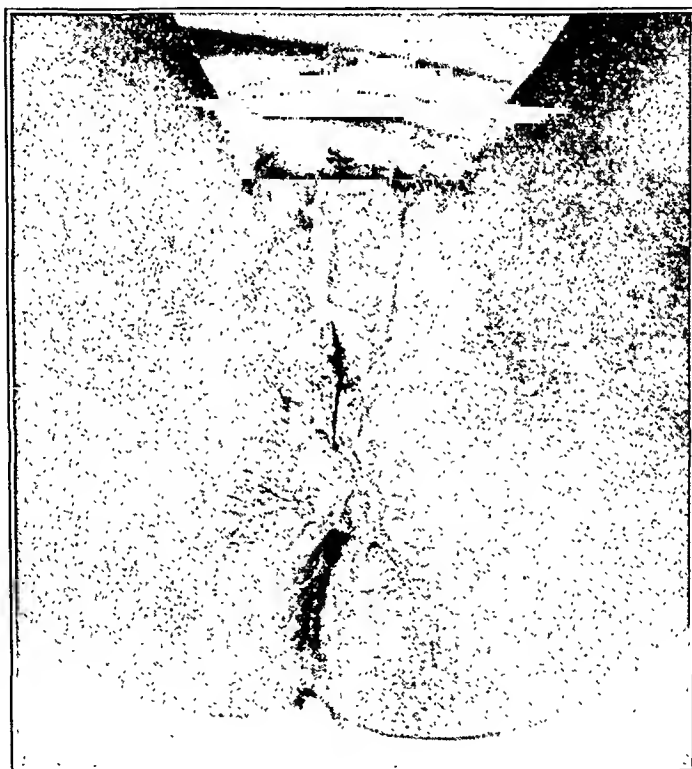


Fig. 2.—Photograph taken June 13, 1938.

The striking features are widely scattered small and large collections of chronic inflammatory cells and granulomatous tissue, of which at least half of the cells are plasma cells and the remainder lymphocytes, mononuclears and occasional leucocytes. These cells are arranged both perivascularly, particularly around lymphatics, but also without relationship to vessels, i.e., wherever skin tissue is found. There is no histologic evidence of malignancy; occasionally an area containing muscle tissue is noted.

Apparently the tumor is essentially a fibroma, with a slight admixture of myxomatous and myomatous tissue, which has slowly grown to large proportions and because of its dependent position has exerted pressure on the vessels, especially the lymphatics, to produce a widespread edema. The presence of so many inflammatory cells and granulomatous tissues points to a widespread irritation which is both marked and continued, although its exact nature remains unknown.

There is a history of a bubo in the right groin discharging pus, and necessitating incision when the patient was fifteen years of age.

At the vulva there was a mass 11 inches in diameter, 23 inches from symphysis to anus, pedunculated, involving both labia majora and minora and the other structures of the vulva, extending from the symphysis pubis to the anus. The tumor was firm, attached to the overlying skin and showed a number of sinuses discharging pus. The vagina could not be entered except with the tip of a finger, while the urethral orifice was completely surrounded by the tumor.

*Laboratory Findings.*—Urine: Specific gravity, 1.025; albumin, 2-plus; sugar, negative; hyaline casts, 5-8 per field; white blood cells, 5-8 per field; Hg, 40 per cent; red blood count, 2,800,000; white blood count, 7,100; polymorphonuclears, 47 per cent; lymphocytes, 50 per cent; monocytes, 3 per cent; Wassermann, negative; Frei test, positive.

The patient was under observation for one week and during this time the local infection was treated by the use of daily antiseptic dressings.



Fig. 1.—Photograph taken two days before operation, May 7, 1938.

On May 9, under avertin anesthesia, the tumor was excised. A rubber catheter was inserted into the bladder and left in situ throughout the operation. The incision was made completely encircling the mass, as for a vulvectomy, so that it extended along the symphysis around both labia and met underneath at the urethra, having the appearance of a double V. The tumor was dissected from the underlying tissue and bleeding was controlled by grasping the bleeders with clamps and coagulating them with the bipolar coagulating current. To relieve tension the skin was undermined and a counter incision was made along the symphysis. The skin edges were then approximated with interrupted silk sutures. An indwelling mushroom catheter was placed in the bladder.

Postoperative course was uneventful except that immediately following operation, the patient went into moderate shock which, however, responded readily within twelve hours to stimulative treatment. The sutures were removed on the eighteenth day and although the skin edges had separated, there was no infection present. The raw areas healed by secondary intention and the patient was discharged on June 15, 1938. Healing was not complete until six weeks later and photographs show how the raw areas became completely epithelized during that time.

After the removal of the indwelling catheter, urination became normal. On return to the follow-up clinic the patient stated that she menstruated normally and has continued to do so regularly. She further reported that she was able to resume normal sexual relations. The patient at present is normal in every respect except for the absence of both labia majora and minora and some local loss of skin pigment.

blood was quite normal. The hemoglobin was 92 per cent (Dare), erythrocytes 5,150,000 and the leucocytes 10,600. A pregnancy test of the urine was not advised.

Operation was performed Aug. 26, 1938. The posterior cul-de-sac was opened without difficulty, and there were no adhesions caused by the previous vaginal operation. There was no free blood in the peritoneal cavity. An ectopic pregnancy  $1\frac{1}{2}$  cm. in diameter was removed from the middle portion of the left tube. Due to the patient's intense desire for a pregnancy and with her consent previously obtained the proximal one-third of the patent tube was left in place. The convalescence was uneventful and the patient left the hospital on the fifth post-operative day, rather doubting, as she expressed it, that anything had been done to her.

This patient's past obstetric history combined with the occurrence of repeated tubal pregnancy is interesting from the standpoint of possible etiologic factors. Her first marriage had occurred sixteen years before. During the second year of this marriage, which lasted only three years, she had given birth to a full-term stillborn baby. This stillbirth was due to a marked fetal abnormality, the main item of which was a marked spina bifida. She had been married four years the second time before the first tubal pregnancy occurred.

It would be rather an unusual circumstance that both husbands should have such a defective germ plasm as to produce three defective pregnancies. This triad might suggest that the primary difficulty was ovular and that the two ectopic pregnancies were the result of a more pronounced fetal defect than the one which interfered with closure in the spina bifida. It might also suggest that this defecation was also a progressive one.

55 E. WASHINGTON STREET

## RUPTURED INTERSTITIAL PREGNANCY AFTER SALPINGO-OOPHORECTOMY ON THE SAME SIDE

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IT IS a well-recognized fact that interstitial pregnancy is uncommon as indicated by the studies of Lavell,<sup>1</sup> who reports but 12 such instances out of 410 cases of ectopic pregnancy at Bellevue Hospital and Wynne<sup>2</sup> who found an incidence of 1.66 per cent interstitial out of 2,405 collected cases. Even rarer, however, is the interstitial pregnancy which follows on the same side on which a salpingectomy has been performed previously. Among those reporting such cases are Lesse,<sup>3</sup> Nache,<sup>4</sup> Hofmeier,<sup>5</sup> Di Palma,<sup>6</sup> D'Errico,<sup>7</sup> Deutsch and Clahr,<sup>8</sup> and von Schroeder.<sup>9</sup> However, the rarest condition encountered is ruptured interstitial pregnancy occurring on the same side on which previous salpingo-oophorectomy has been done. I have recently encountered such a case and after an extensive search of the literature have found only seven others identical with it, and these are reported by Richardson,<sup>10</sup> Campbell,<sup>11</sup> Douglas,<sup>12</sup> McIntyre,<sup>13</sup> Meyer,<sup>14</sup> and Naujoks<sup>15</sup> (2 cases). One must be careful not to be misled by reports of cases in which a stump of the isthmus of the tube has been left in which subsequent pregnancy has occurred.

M. L., aged 35 years, negress, was operated upon Jan. 10, 1937, at Barnes Hospital by the resident gynecologist for ruptured ectopic pregnancy in the ampulla of the right Fallopian tube. Right salpingo-oophorectomy was performed, and in addition a pedunculated myoma  $2\frac{1}{2}$  inches in diameter which was arising from the right cornu of the uterus was excised.

The patient was readmitted to Barnes Hospital Jan. 12, 1939 on the general surgical service with a diagnosis of partial intestinal obstruction made by the referring physician.

Although the preponderance of fibrous tissue justifies a diagnosis of fibroma of the vulva, the presence of so many inflammatory cells and the abundance of granu-  
lomatous tissue might be due to lymphopathia venereum or to a syphilitic infection. However, a definite choice between these two diagnoses is impossible, as the history and laboratory records could support either thesis. We therefore feel that the future progress of this patient will be the clarifying factor regarding the relation of syphilis or lymphopathia venereum in this growth.

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44 EAST 78TH STREET  
430 EAST 86TH STREET

## VAGINAL REMOVAL OF REPEATED ECTOPIC PREGNANCY\*

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EARLY diagnosis and removal by the vaginal route of ectopic pregnancy has become an established procedure in many American and European clinics. It is rather unusual to find patients who have developed an ectopic pregnancy for the second time. It is still more unusual to have the opportunity of treating a patient in whom recognition of an ectopic pregnancy, twice within a period of three years, could be accomplished in the early stages and vaginal removal of both of the fetuses performed.

Mrs. L. S. (No. 315732). The patient was admitted to the Presbyterian Hospital, April 7, 1936 on the medical service. At that time she was 32 years old, had been married sixteen years, and had one child twelve years before. This child was stillborn at term due to a spina bifida.

The complaints on this admission were relative amenorrhea of sixty-two days' duration. During this time, there had been only two days when slight vaginal bleeding was noticed. Excessive fatigue had been present. Aching through the pelvis had become more pronounced. The morning of admittance severe right-sided pelvic pain had occurred. At that time the erythrocytes numbered 4,650,000 and the leucocytes on repeated examinations ranged from 6,900 to 10,300. The patient was discharged from the hospital on April 9, 1936 and readmitted on the gynecologic service April 20, 1936. The patient thought she had menstruated April 13 and 14. There were no complaints. There was a tender palpable mass in the region of the right adnexa and the Zondek test was positive.

Operation was performed April 20, 1936, and an ectopic pregnancy of the infundibular portion of the right tube with several large blood clots was removed through a posterior colpotomy incision. The ectopic sac measured  $5\frac{1}{2}$  by  $3\frac{1}{2}$  cm. The opposite tube and ovary were grossly normal. The uterine scrapings were not profuse and histologically revealed only a moderate decidual reaction. The convalescence was entirely normal and the patient left the hospital on the seventh postoperative day.

The patient was admitted to the hospital again Aug. 25, 1938, complaining of a weak feeling in the region of the vagina and a brownish vaginal discharge of one week's duration. This spotting had begun at the time she had expected her regular menstrual period. There had been no amenorrhea. There was slight pain in the left lower quadrant. No enlargement or uterine changes could be palpated on vaginal examination. There was a definitely increased tenderness in the region of the left Fallopian tube. The patient was undecided whether her symptoms resembled those of her previous experience. The examination of the

\*Presented at a meeting of the Chicago Gynecological Society, April 21, 1939.



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## ENDOMETRIOSIS OF THE ROUND LIGAMENT SIMULATING HERNIA

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(From the Surgical Service of the Memorial Hospital)

**E**NDOMETRIOSIS in its protean manifestations gives rise to a confusing clinical picture at times, and it is the purpose of this paper to record an instance of rather unusual site of endometrial tissue.

Endometrial tumors or "implants" as Sampson calls them have rather widespread distribution within the peritoneal cavity, commonly involving the ovary, the peritoneum, the rectovaginal septum, etc. Less frequently they occur in the umbilicus, in the round ligaments and in laparotomy scars. The method of extension of the process to the round ligament and inguinal region is as much in dispute as the etiology of endometriosis in general. The lesion of the round ligament may consist of a more or less solid tumor, an adenomyoma, or may be in the nature of a hemorrhagic cyst. The frequent association of hernia and inguinal endometriosis has been a matter of comment with several writers. Errors in the differential diagnosis between hernia and inguinal endometriosis are not infrequent. Cullen who described the first case of inguinal endometriosis in 1896 thought his patient had a hernia; likewise Sampson, Selmitz, Christopher, Neel and others made similar errors.

Involvement of the intraperitoneal portion of the round ligaments gives rise to no important symptoms; involvement of the extraperitoneal portion does. With endometriosis of the round ligament usually a tumor of the inguinal region occurs; this may be either cystic or solid; it may or may not be painful; it will disappear when the patient lies down, if it is the cystic type, and there may be an impulse on coughing; the solid type of lesion as a rule is not reducible.

From this brief description it becomes apparent how inguinal endometriosis may readily be mistaken for a hernia.

### CASE REPORT

The patient was a 34-year-old female who had never been pregnant, although married for twelve years. She complained of a "bunch" in the right groin of five years' duration. At times this "bunch" would ache, but it became most painful during menstrual periods. In addition there was a "bunch" in the left groin but this one never pained; both of these disappeared when the patient lay down. This patient had commenced to menstruate at the age of 13 but was very irregular until age 18, when she established a twenty-one-day cycle with each period lasting seven days and being moderately profuse. Until five years ago there had been no pain at menstruation; at that time pain made its appearance and has gradually increased until now it is severe enough to necessitate opiates for relief. The last period had terminated two days prior to examination. There was no history of bladder or rectal disturbance. The past history was irrelevant except for attacks of paroxysmal tachycardia.

Examination disclosed a well-nourished and well-developed individual. The abdomen showed some tenderness in both lower quadrants. No masses were made

Previous to the first operation the patient had had 3 miscarriages, 3 abortions, and 3 normal deliveries, and 4 months subsequent to it she became pregnant and had a normal delivery in February, 1938. Her last menstrual period began Dec. 5, 1938 and about three weeks later she began to notice occasional nausea. Jan. 8, 1939 she was seized with terrific pain in the lower abdomen and became extremely weak. No vaginal bleeding occurred. She was put to bed and in a few hours began vomiting. A physician was called whose treatment consisted of repeated enemas. Pain, vomiting, and abdominal distention persisted up until the time of admission to the hospital on the fourth day of the illness.

*Physical Examination.*—The patient was a moderately obese, 37-year-old negress who was acutely ill. Temperature  $37^{\circ}$  C., pulse 100, and blood pressure 96/40. The abdomen was markedly distended and tympanitic, presenting a subumbilical, midline operative scar. There was moderate muscle guard over the entire abdomen and likewise marked tenderness to light pressure, particularly over the lower abdomen. Neither visible nor audible peristalsis was present, and heart sounds were not heard over the abdomen. Upon vaginal examination the cervix was perhaps slightly softened, the fornices not bulging; however, the patient was so exquisitely tender that nothing further could be learned. Rectal examination gave no additional information.

*Laboratory Findings.*—White blood count, 18,700; red blood count, 3,410,000; hemoglobin, 65 per cent. Urine contained albumin 1+, diacetic 3+, and numerous casts.

I regarded ruptured ectopic pregnancy with resultant paralytic ileus as the most probable diagnosis. The patient was prepared for operation with parenteral fluids and continuous gastric siphonage for several hours.

Under general anesthesia, a low left rectus incision was made, and upon exposing the peritoneum, it was apparent that there was a large amount of free blood beneath it. Upon opening and inspecting the peritoneal cavity, the left Fallopian tube and ovary were found to be entirely normal, but hanging loosely from the region of the right uterine horn was an ovisac about the size of a golf ball and from the deep depression remaining in the horn, active bleeding was taking place. The ovisac, containing a 1.5 cm. embryo, was removed and the horn closed with several rather deeplocked stitches of chromic catgut. The medial superior portion of the broad ligament was tacked over the raw surface of the horn. The body of the uterus was about twice normal size and softened. A Penrose-drain was placed in the bottom of the pelvis, after as much free blood and clots as possible had been removed, then routine closure was carried out. Five hundred cubic centimeters of citrated blood was given during operation. The patient was kept on continuous gastric siphonage for three days postoperatively, until peristalsis had become re-established, and her recovery was uneventful.

#### DISCUSSION

This case is of interest for at least three reasons: It is extraordinarily rare, there being only 7 identical, authentic cases previously reported. We were confronted with a difficult diagnostic problem in explaining the cause of the obvious paralytic ileus of four days' duration. The case opens up a field for speculation as to where the ovum became fertilized, and how it became implanted in the interstitial or mural portion of the tube on the same side on which salpingo-oophorectomy had been performed previously. The existing possibilities are that the ovum from the remaining left ovary passed down the left tube into the uterine cavity and then entered the uterine orifice of the right tube stump, having been fertilized at some point along this course, or else the ovum migrated across the peritoneal cavity to enter a patent right tube stump, being fertilized either in the peritoneal cavity or in the stump.

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rhage. The left tube was markedly thickened; the left ovary could not be identified. A separate structure consisting of a thin walled cyst containing scro sanguineous fluid was present.

Microscopically there were found in both broad ligaments, numerous foci of endometrial tissue with acini containing recent and old blood. The distal end of the appendix showed endometrial implants with dense scarring. The endometrium of the fundus uteri showed benign hyperplasia. Sections of the nodules of the myometrium showed the typical histology of leiomyoma.

For the microscopic study of the tissues, the author wishes to thank Dr. John J. Clemmer, Director of the Laboratory.

302 STATE STREET.

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## CAVERNOUS HEMANGIOMA OF OVARY IN A GIRL TWELVE YEARS OF AGE

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VASCULAR tumors are common on the skin and mucous surfaces, occurring on the head, neck, trunk and extremities. However, visceral vascular tumors are rather rare, only a few cases being reported in the literature, these tumors originating essentially by proliferation of vascular walls or from a matrix of angioblasts. The cavernomas are characterized by irregular blood spaces lined with endothelium, and formed by a connective tissue stroma. The growth may appear as a diffuse mass, but more often as a circumscribed tumor, having a distinct capsule. Visceral angiomas usually occur in the form of cavernomas. Such cavernomas were reported by Rosenthal, Langer and Keene, occurring in the liver. Cases have also been reported where cavernomas have occurred in the spleen and in the alimentary canal, of which there are about 20 cases described in the literature. Cavernomas of the ovary are rather rare since not many have been reported. J. P. Shearer reported a case in a child 3.5 years old. R. Keller reported a case in a woman 36 years of age. In 1927 R. H. Jaffe, reported a case of multiple hemangiomas of the skin and internal organs. Our case is a cavernoma of the left ovary occurring in a girl 12 years of age.

Patient, R. C., 12 years old, gave a history of having pain in the pelvis for the past two weeks. The pain was more or less continuous, and, at times, of a twisting character. During this time she had nausea and vomiting. Constipation was present and enemas were not effectual. She had one period prior to the onset of this condition, but a regular menstrual cycle was not yet established since the patient was only 12 years old. However, she was seen by several doctors and one made a diagnosis of pregnancy, in view of her amenorrhea. On admission to the hospital her temperature was 99.6° F., and pulse 92. A complete blood count showed: Red blood count, 3,950,000; white blood count, 9,200; hemoglobin, 12 gm. The differential count showed polymorphonuclear leucocytes, 78 per cent; and lymphocytes, 32 per cent. The Schilling count was as follows: segmenters, 74 per cent; stabs, 4 per cent; juveniles, 0 per cent; myelocytes, 0 per cent. Urinalysis showed a trace of albumin, no sugar, and the microscopic examination revealed 8 to 10 leucocytes to the high power field.

Physical examination showed a rather tall young girl for her age, but she appeared undernourished and somewhat emaciated, probably the result of her two weeks' illness. Her features were pinched, showing evidence of constant pain. The abdomen was flat and tenderness was elicited on palpation over the whole hypogastric region. No masses could be felt in the abdomen by external palpation and no rigidity was present anywhere over the abdomen. A rectal and vaginal examination

out in the inguinal regions while the patient was on the examining table. Bimanual examination revealed a retroflexed, adherent uterus, about twice normal in size. There were tender masses in both fornices. With the patient standing, a soft, easily reducible mass made its appearance in the right inguinal region; the mass transmitted an impulse on coughing; the left inguinal region revealed no mass and no impulse on coughing.

At operation, the usual picture of rather extensive endometriosis was found. The uterus was enlarged and densely adherent to the rectum. The left tube and ovary were firmly attached to the posterior aspect of the fundus. The serosal surface of the uterus and the pelvic peritoneum were studded with typical endometrial implants. The broad ligaments showed old and recent hemorrhages. There were hemorrhagic cysts of both round ligaments, the one of the right side being considerably larger. The latter was about 7 cm. in length and 2 cm. in diameter. The appendix was buried in the right side of the pelvis with its tip involved in the endometrial process. A panhysterectomy with removal of both tubes and

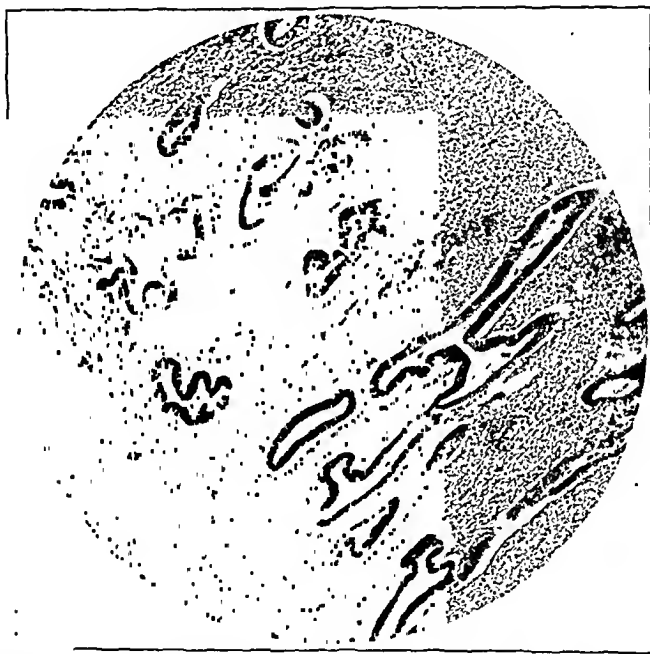


Fig. 1.—Section from left round ligament showing hyperplastic endometrial acini in typical endometrial stroma. The stroma contains recent hemorrhage.  $\times 60$ .

ovaries, both round ligaments and the appendix was done. The cystic round ligaments were dissected out as completely as possible through the internal rings. The patient's postoperative course was uneventful except for a prolonged attack of paroxysmal tachycardia, and she left the hospital on the sixteenth day with the wound healed. Final examination of the patient was made fifteen months after operation at which time nothing of note was found; the "bunches" in the groins had not returned.

*Laboratory Report.*—The specimen consisting of the entire uterus, tubes, and ovaries, weighed 260 gm. The myometrium of the fundus contained several leiomyomas, the largest of which was 2.5 cm. in diameter. The endometrium was thickened and polypoid but showed no gross invasion of the muscle. The right tube was grossly normal. The right broad ligament was thickened and hemorrhagic. The right ovary measured 4 by 2.5 by 1.5 cm.; it contained a hemorrhagic corpus luteum and simple follicular cysts. The left broad ligament was markedly thickened and indurated and contained areas of old and recent hemor-

In addition to the foregoing, we would like to mention three other cases of aplasia of the uterus which have come to our attention during the past three years.

CASE 2.—R. F., Portuguese, aged 23 years, came to one of us (H. E. B.) June 4, 1937, for treatment of a Bartholin's abscess of gonorrheal origin. Vaginal examination revealed a total absence of cervical os, and no uterine body could be felt. Intravenous pyelograms were done to see whether any congenital malformation of the kidneys might also be present. The films showed no left kidney shadow, while the right kidney shadow was normal. Nothing further was done at this time.

On Aug. 1, 1938, she was operated upon by Dr. R. J. McArthur at Wailuku, Maui, for the relief of lower abdominal pain. At laparotomy, two rudimentary uteri were found, one on each side of the pelvis. The left uterus and oviduct were represented by a small tube with an ostium corresponding to the fimbriated end of a Fallopian tube. The embryonic uterus coursed downward along the free edge of the broad ligament gradually disappearing in the vicinity of the bladder in a small fibrous cord. The right uterus was similar to the left, only larger, had no ostium, and appeared to be large enough to menstruate. Both uteri were excised. The ovaries were left alone as they were normal except for some small cysts which were punctured. A constricted appendix was removed. Recovery was uneventful.

CASE 3.—Mrs. M. C., aged 26 years, Portuguese, complained of vague pain in the abdomen. Incidental vaginal examination revealed no visible or palpable cervix or uterine body. She stated that she had been operated upon by Dr. W. T. Osmer of Wailuku, Maui, in 1926, for acute appendicitis. Although hospital records have been lost, Dr. Osmer writes that he remembers a very rudimentary uterus was found, consisting merely of a small knob. The ovaries were small but recognizable. Other details are lacking.

CASE 4.—A nurse, aged 23 years, German-Portuguese, single, tall, masculine type, flat breasted, was operated upon by Dr. C. L. Phillips of Hilo, Hawaii, for acute appendicitis.

At operation, an inflamed appendix was removed. Pelvic inspection revealed nothing resembling a uterus. Two small rudimentary tubes were joined in the midline along with two poorly developed round ligaments, giving the appearance of a complete supravaginal hysterectomy. There was a very small, buttonlike piece of tissue in the vaginal vault which seemed to represent the cervix. No true ovarian tissue was seen, though it was believed that a slight thickening at the end of each tube may have been ovary.

We wish to thank Dr. Osmer and Dr. McArthur of Wailuku, Maui, and Dr. C. L. Phillips of Hilo, Hawaii, for permission to report the three additional cases to supplement our own.

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was made under nitrous oxide and oxygen anesthesia. The hymen was very much relaxed so that a small speculum was easily inserted. The vaginal mucous membrane was somewhat congested and a small amount of mucopurulent discharge was present. The cervix was eroded. A smear of the cervical and vaginal secretion was negative for gonococcus. On bimanual examination the cervix was hard to the touch, the uterus was small, hard and anteverted. A large mass the size of a grapefruit was present in the pelvis and more in the left adnexa. A diagnosis was made of ovarian cyst, probably with twisted pedicle, because of the severe pain. On the following day under ether anesthesia the abdomen was opened and a large ovarian cyst twisted on its pedicle was found on the left side. The cyst was easily separated from adjacent tissues but incorporated the tube. A left salpingo-oophorectomy and appendectomy was done. The cyst was about 12 cm. in diameter and hemorrhagic in color.

The histopathologic report was as follows: *Gross*: Specimen was apparently a large cyst with an attached Fallopian tube and an appendix. The appendix was 3.5 cm. long and 0.8 cm. thick. The wall of the appendix was thick, mucosa edematous and formed one-half the wall. The lumen was very narrow. The cyst was multilocular, contained a sanguineous fluid; one portion of the wall at its thickest region was 1.8 cm. thick and composed apparently of a blood clot. The Fallopian tube was filled with blood down to the cyst and its thickest region was 2.0 cm. *Microscopic*: The tissue labeled ovarian cyst was composed of numerous large and small blood vessels with no intervening supporting tissue. The blood vessels were filled with red blood cells. Periserosal tissue adjacent to the cyst was edematous and was infiltrated with inflammatory cells, mostly plasma cells and pulp. These sections were covered so densely with red blood cells that no underlying tissue could be seen.

*Diagnosis*.—Cavernous hemangioma of ovary with diffuse hemorrhage.

5505 SPRUCE STREET

5012 SPRUCE STREET

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## APPARENT CONGENITAL ABSENCE OF UTERUS

H. E. BOWLES, M.D., AND C. M. BURGESS, M.D., HONOLULU, T. H.

(From "The Clinic")

COMPLETE congenital absence of the uterus or of the vagina, or of both, has been reported by daCosta,<sup>1</sup> Veach,<sup>6</sup> and Walters and Qualls.<sup>7</sup> It is exceedingly unlikely, however, that there was an absolute absence of all vestiges of these parts. Graves<sup>3</sup> and Wharton<sup>8</sup> emphasize that there is always some rudimentary tissue present even if it exists only as a fibrous band.

The following case of apparent absence of the uterus was operated upon by one of us (C. M. B.) on April 20, 1939:

CASE 1.—R. L., an eleven-year-old Korean girl, was admitted to The Children's Hospital, Honolulu, for removal of an interval appendix.

A right rectus incision was used and, following the removal of the subacutely inflamed appendix, it was noted that the broad ligament of one side swept across where the uterus should have been and fused with its fellow from the opposite side of the pelvis. No thickening was present which might have been interpreted to be the uterine body. The tubes and round ligaments were joined in the midline and were unusually well developed for a girl of eleven. The ovaries were also normal and prominent. Subsequent vaginal examination through an otoscope revealed no apparent cervix, and on rectal palpation, no uterine body could be felt. Nothing was done other than appendectomy and examination of the pelvic contents. Convalescence was uneventful. Aside from the congenital anomaly, this girl looked like any normal female.

heated air is circulated through a special shaped thin-walled rubber bag which is inserted in the vagina in a collapsed state and then inflated with air so as to distend the vagina. This distention of the vagina serves a two-fold purpose, first, the tissues are "ironed-out"; all of the folds and rugae are flattened, thereby bringing the rubber bag in immediate contact with the tissues, and, second, due to this fact, the heat is radiated uniformly over a large area to the surrounding structures thereby eliminating so-called "hot spots."

The heated air is continuously circulated through the bag producing a uniform temperature throughout and an even distribution of the heat. Therefore the maximum tissue temperature during any time of the treatment is never higher than the temperature recorded by the thermometer which extends into the bag. The maximum heat concentration instead of being over a small area will be uniform over a large area in direct contact with the applicator bag. Any other type of electrode which is used in the vagina without producing distention of the cavity will only have point contact, or at best, a small area of contact with the tissues, thereby resulting in the possibility of the heat concentrating at this spot and producing a burn.

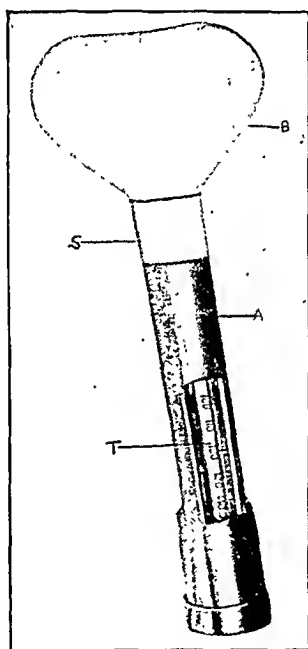


Fig. 2.—B, Bag; S, sleeve; A, applicator; T, thermometer.

The machine is small and consists essentially of a fan which circulates air through the applicator bag. The air is heated by an electrical unit, the temperature being controlled automatically by a thermostat set for any desired temperature. Temperatures up to 130° F. can be used, although lower temperatures for longer periods of time seem to be more beneficial. The thermometer which extends into the bag (Fig. 2) is protected by a bed of rubber. Broken thermometers can be readily replaced. A hand-operated rubber bulb similar to that used on blood pressure machines is used to inflate the rubber bag, thereby giving any degree of smooth and even distention. The pressure which is approximately 1 to 1.5 pounds is indicated on the pressure gauge. A time clock is incorporated in the machine so that the treatments can be timed for any desired period.

Inasmuch as the bag is distended with air and since the weight of the contained air and bag is negligible, being less than 0.25 ounce, there is no pressure or feeling of weight in the pelvis to produce any discomfort to the patient during the treatment, as there is with a bag filled with water, the weight of which is approximately 0.5 pound. Observations and reactions of patients disclose a marked feeling of in-

## AN IMPROVED METHOD FOR APPLYING PELVIC HEAT USING AIR

LOUIS B. NEWMAN, M.D., CHICAGO, ILL.

IN USING any device for producing heat in any part of the body, two very important requirements must be fulfilled in order to treat the patient safely and effectively without the danger of burns and their associated effects. First, the maximum tissue temperature at any time during the treatment must be known, and, second, the point or area of maximum heat concentration in the tissues must also be known.

A new improved apparatus for producing dry heat has been developed by the author, and has been used for several years in the treatment of pelvic inflammatory conditions. This machine (Fig. 1) fulfills the requirements stated above. With it,

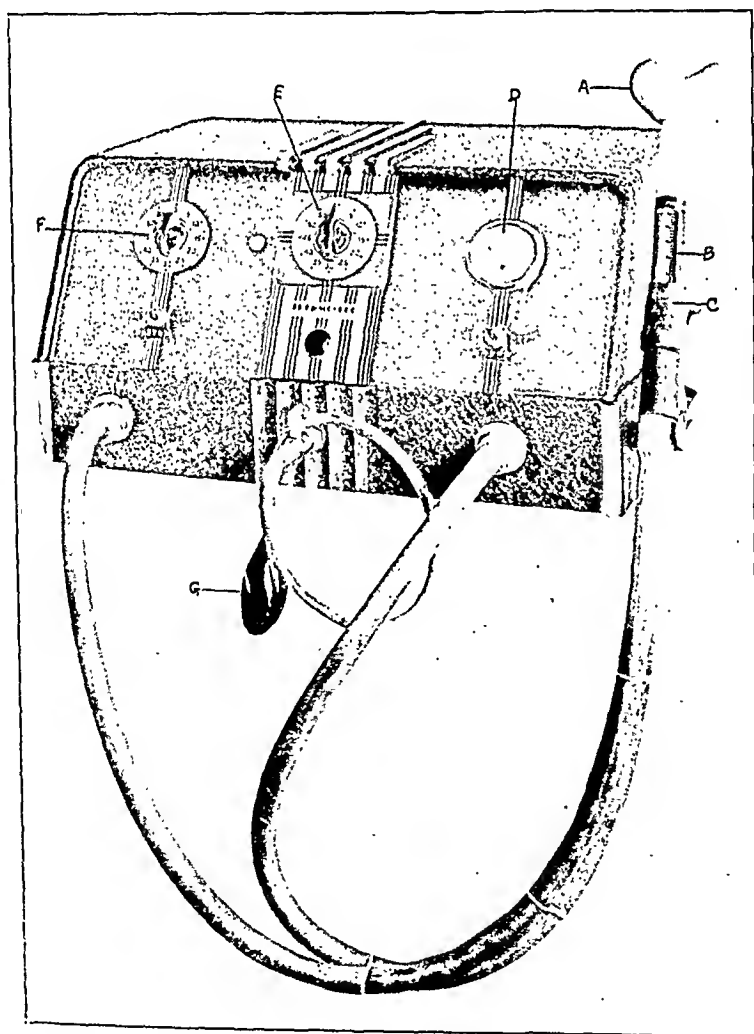


Fig. 1.—A, Bag; B, thermometer; C, applicator; D, pressure gauge; E, time clock; F, temperature control; G, rubber bulb.



## Editorial

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### American Congress on Obstetrics and Gynecology

THE first American congress devoted to this branch of medicine was held in Cleveland, Ohio, from September 11 to 15. Its success may be measured by the attendance and the countrywide contributions to its program. The paid membership totaled over 2,500, but the total number of persons who attended the session and visited the exhibits was probably well over 5,000. Physicians, nurses, public health workers, hospital administrators and educators crowded the various meeting rooms and exhibition halls and there were many expressions favorable not only to the present enterprise but to its continuance in future years. The program included over 120 papers presented in sections devoted to medicine, nursing, public health, hospitals and education, and each of these conducted round table discussions. There were also five joint afternoon sessions and an equal number of evening meetings open to the general public.

One of the primary objects of the Congress was to bring together all interested groups and the large attendance furnished ample proof of the scope of this interest. It was remarkable that so many workers, eminent in their various fields, could be brought together at this initial gathering and that so many outstanding contributions were made available to those who came to Cleveland on this memorable occasion. Individual references to the many addresses are impractical but the general summary of the work of the Congress presented on another page by its General Chairman will afford an insight into its important accomplishments.

Great credit is due to the executive committee of the American Committee on Maternal Welfare, which promoted the Congress and to its Chairman, Dr. Fred L. Adair, as well as to the various sectional groups, for the excellent arrangements which made of this gathering an outstanding contribution to the advancement of American obstetrics and gynecology. The participating organizations are to be commended likewise for their material support and similar commendation must be extended to the commercial exhibitors and to those who made the scientific and technical displays of such value and of such high standards.

The Congress will go down in American medical history as a signal accomplishment which, it is hoped, may be repeated at definite intervals.

crease in the weight of liquid-filled bags as the treatment progresses. This sensation is not experienced when the air-filled bag is used. If the bag should tear during a treatment, the patient will not be burned, as the bag merely collapses; there is no escape of hot water. A double seal sleeve is incorporated on the applicator so that torn bags can be easily and quickly replaced, no cementing being necessary.

The technique in giving treatments is very simple. The deflated bag is lubricated and inserted into the vagina. The bag is then inflated by means of the rubber bulb, the amount of distention being governed by the comfort of the patient. A pillow placed under the patient's knees also supports the applicator holder so as to eliminate any pull on the pelvis. The time clock is set for the length of treatment, the temperature control is set for the desired temperature, the switch is turned "ON" and the treatment is begun. No preheating is necessary as the air in the bag at the beginning of the treatment is never lower than room temperature and will not chill the patient. During operation, the air is heated rapidly to the desired temperature. As the volume of air increases when it is heated, the bag will expand slightly and thereby result in more perfect contact with the surrounding tissues which, by this time, have become softer and more pliable due to the heat. If the patient complains of too much distention, a little air is permitted to leak out by opening the air valve on the pressure bulb. At the end of the treatment, the switch is turned "OFF," the bag is deflated and withdrawn from the vagina. There is nothing to spill or leak to burn the patient or soil the bed. The applicator holder together with the bag and specially constructed thermometer (Fig. 2) can be sterilized as a unit, either by boiling or immersing in a suitable antiseptic solution. By using an additional bulb, a massaging effect can be obtained if desired.

When the applicator is removed, the machine may serve as an excellent source of dry-heated air which can be used for therapeutic purposes.

With this machine, uniform dry heat together with distention may be safely given to both the male and female pelvis over long periods of time. The maximum temperature and the area of maximum heat concentration are known at all times during the treatment. This, coupled with the ease of operation, insures a high degree of safety, efficiency, and comfort to the patient. By circulating air through a cooling coil, low temperatures may be secured in the rubber bag.

5146 WEST 25TH STREET

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Howkins, J. and Brewer, H. F.: Placental Blood for Transfusion, *Lancet* 1: 132, 1939.

The authors were able to collect an average of only 47 c.c. of placental blood in 50 consecutive cases of normal labor. Twenty-two per cent of the collections were contaminated when checked for sterility at intervals of six to fifteen days. The organisms found were *B. subtilis*, *B. coli*, *Staph. albus*, and *B. pyocyaneus*. The ordinary personnel of the labor ward was used in the collection. The writers conclude that this source of blood is uneconomical and unsafe.

CARL P. HUBER.

Halbrecht, J.: Transfusion With Placental Blood, *Lancet* 1: 202, 1939.

The author reports 116 transfusions of blood obtained from 520 placentas at the Beilinson Hospital, Palestine. Four reactions occurred of which 3 consisted of a chill and 1 of dyspnea and tachycardia. Blood preserved in 3.8 per cent solution of sodium citrate stored at 4 or 5° C. for as long as fourteen days was used. An average of 50 to 60 c.c. of blood was drained from each placenta with a maximum of 160 c.c. The results are equal to those obtained with fresh blood and placental blood is looked upon as an important source of blood for transfusion.

CARL P. HUBER.

free and equal. Free doubtless in our continent so far as human contacts and nature's laws permit, but, while politically equal in theory, at least they certainly are not equally endowed physically, mentally, or psychologically. We could all agree that among us everyone should be freed of avoidable hereditary and environmental handicaps, so that all could have as nearly as possible an equal opportunity and a fair start in life.

We all recognize this ideal in our sports which are governed by certain rules which enable us to compete on a fair basis, with an umpire enforcing the rules. In civil life there are certain laws, with the courts acting as the umpires. Unfortunately, the laws are not always equitable and work out unfairly, and our judges are not always unbiased. Government is an experiment and there are few valid controls; democracy is being tried and is slowly advancing to the goal of equal opportunity and the maximum of happiness, life, and liberty to all.

This introduction may seem far afield from the objectives of the Congress, but if one considers carefully what maternal care means, the purpose of these few comments is apparent. The basis of our life depends on equal opportunity for every one of us, and the future of our institutions and country depends upon the development of equality for all mothers and their babies. The accomplishment of this involves the control of both hereditary and environmental influences, all of which are not completely understood. Time will bring added knowledge, but in the meantime we have much to do in securing universal application of the knowledge which we already possess.

It has been conclusively proved that the more general application of the knowledge we possess to the care of mothers and their babies can and has reduced our national, state, and local mortality rates. However, it is necessary to emphasize again and again that a reduction of the mortality rates is only a partial answer to the problems. Death is a very concrete criterion upon which we can base certain factual data from which some conclusions can be drawn. The mortality rate is also an index of a larger morbidity rate which is of tremendous importance. Much disability and a shortened life of a mother or of a baby can be charged to the lack of proper obstetric care. Death is the natural sequence of life and all individual physical life terminates after a specified cycle. While we live, health is most desirable, and no one person and no society can look with equanimity upon life with avoidable illness or one ending in premature death.

The groups represented here are primarily concerned with health and with health education. The discussions and the data presented in our programs and by the movies and in the exhibits have portrayed certain information to us and to the public through the press and the open public meetings. These data may be classified into the following categories: The present status of our knowledge about the mother, the fetus, and the newborn; the present methods of applying this knowledge for the benefit of all; the revealing of possible errors and of definite gaps in our existing knowledge and the discussion of ways and of means to eliminate these errors and to discover the proper approach to the solution of unsolved problems have all been considered more or less fully.

There is the tremendous task of selecting the best methods of applying our present knowledge and of determining how these programs can be universally applied. In passing it may be well to observe that certain fundamental principles are well established and essential to the success of any plan and while the methodology or technique of application may vary, the basic principles remain unaltered. For example, no one could at present deny the necessity for clean aseptic deliveries, though there might be a difference of opinion as to the best means of preventing puerperal infection.

The groups represented here are doctors, nurses, public and voluntary health agencies, institutions for medical and nursing service and for education. Our common objectives are those that pertain to the welfare of women, chiefly mothers, and the babies, especially the newborn. Our objectives are ultimately the same though our approach, viewpoints, and methods of solution may differ. It is vital that we agree on certain fundamental principles, even though the methods of application and of accomplishment may differ. We could all doubtless agree that care of mothers and babies which is adequate to conserve individual and community health and life is essential.

# Department of Maternal Welfare

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CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

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## AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY\*

### GENERAL SUMMARY AND COMMENTS

FRED L. ADAIR, M.D., GENERAL CHAIRMAN, CHICAGO, ILL.

THE groups assembled at this first congress on obstetrics and gynecology had a common purpose and were actuated by a motif for the prevention and correction of conditions which lead to the disability or death of mothers and their babies. They were gathered here to promote those conditions of living which are inherent in our institutions and in our human rights; that is, the equal opportunity for life, liberty, and the pursuit of happiness. It is our belief that there are two fundamental objectives which are closely coordinated and are essential to the attainment of these goals. We might state succinctly that without proper physical, intellectual, and psychical health, there is no satisfactory education, and without such education about ourselves there cannot be optimum health.

Past as well as existing episodes, individual as well as group tragedies, personal as well as impersonal experiences, national as well as world cataclysms bring forcibly to mind the importance of having fewer abnormal, more normal, and an abundance of superior personalities.

Democracy and civilization have no need for abnormally developed persons with perverted ideas and behavior. Democracy needs an abundance of normally, of socially and of humanistically minded individuals among its citizens. The world needs superior right-minded and great leaders who are capable of thinking through and of developing not only plans for national but also for international welfare. The foundations of the past were laid by our ancestors, the structures of the present were reared by our fathers. We are occupying what they and we have built. The bridges to the future over which those yet to be born must travel are being devised now. It is for us to see that those structures are so well planned that they cannot collapse and be swept away by rising torrents. The future depends largely upon what is done now. It is important for those of us who believe in our nation and in its institutions to recognize that the mothers and their babies are the first and last line of defense. We wish no one from within or from without to interfere with or to dictate the course of development of our institutions and our country. We have no desire to hinder other peoples who believe in differing types of development so long as they interfere in no way with our peace and our freedom. We can and should defend the mothers and babies, both born and unborn, to the last trench both in peace and in war.

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The laws of heredity and of environment are the most potent factors in the life of any individual. The father is an equal hereditary influence, but he has nothing to do with fetal environment except indirectly through the mother who determines the intrauterine life of the fetus. The newborn, the early and later infant and childhood life is largely influenced by maternal environment. Doubtless this is the most powerful and lasting influence which affects the development of our bodies, of our minds, and of our characters.

Years ago, measured by the individual duration of life, but minutes ago in terms of the development of human life, the idea was set forth that all men are created

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\*Presented at the closing session of the Congress, September 15, 1939.

For lack of space this address can only be published in part but will be supplied in full in the author's reprints.

and infants. For the mothers as they must supply the proper hygiene and nutrition not only for themselves but also for their infants especially during pregnancy and lactation.

The period of growth and development is vital as the fetus, newborn, infant, and child must have in addition to the materials essential for maintenance, those substances fundamental for growth. Growth is a process which is affected by both hereditary and environmental factors. Growth and development do not follow a straight line but a jagged one because of spurts which occur at various epochs in the life cycle. If essential elements are lacking at crucial periods, an arrest of growth may occur which cannot be compensated later. This means a permanent lack of optimum development. Interference with skeletal development and subsequent bony deformity due to lack of certain nutritive elements and of proper hygiene is one of the most striking illustrations which is obvious even to the casual observer. It is curious but nevertheless true that the availability of the essentials is not the only difficulty encountered in securing proper hygiene, food, etc., for mothers and infants. Habits and customs have such a strong hold upon our lives that many of us follow them blindly in spite of obvious errors and even though the proper hygiene and food are accessible. The problems then are not always simple and people have to be not only educated but re-educated. It is essential not only to remove factors leading to erroneous living but also to introduce a program of right living. In other words, one's life has often to be reconstructed and rehabilitated. This cannot in many instances be accomplished in one generation. If we do not worship our ancestors, we frequently cling to their customs and our own habits.

It might just as well be recognized that all persons are not well adapted for parenthood. In some instances reproductive life may be detrimental to a woman and hasten the inevitable end of her life. Under other circumstances the infant itself may be a poor product and be useless or harmful to itself and to others. It is also well known that fertility differs greatly in different persons and that some individuals are incapable of reproduction. This may be a great tragedy in their lives. Many can be made fertile—some remain sterile. Probably the greatest tragedy in a woman's life is the rejection of an opportunity to have a baby, and as a result acquire a permanent sterility but retain a longing for a subsequent childbirth. Much can be done now to cure infertility and more will be learned in the future.

Repeated or habitual abortions sadden many women's lives, but scientific advances in endocrinal therapy offer real hope to many for a successful pregnancy. The problem of abortion is a vast one, and no one really knows how many occur each year, but 750,000 is a not unreasonable estimate. The program of prevention is a very sizable one, and it can be solved only by proper education and medical care. The problem of abortion is much larger than the saving of the lives of 4,000 women and their lost pregnancies yearly. Many women are thus invalidated and many become sterile. The care of patients having abortions is one of the important phases of prenatal care.

Prenatal care involves more than medical and nursing attention, as many sociologic and economic factors are related which doctors and nurses cannot solve. They, as well as others, need compensation for their work and unfortunately our present unbalanced economic system places many of our citizens in a marginal or submarginal economic status so that their income must be increased or supplemented. How these various difficulties can best be overcome no one has yet proved. An ultimate solution is essential and progress toward this goal must be made as rapidly as possible. Adjustments in our economic and sociologic life which will promote education and health among us are vital for the continuation of our democratic institutions and country. It can be reiterated that the success or failure of our civilization depends largely upon our ability to progressively improve our mothers and babies physically, intellectually, and psychologically. This depends largely upon continuity of programs and plans. One step leads to another and thus pre-conceptional is followed by prenatal care. It is impossible to state the details of prenatal care at this time, but it is important to bring about a situation where every mother receives it in her home, in the clinic, or in the hospital as circumstances require.

What then are the fundamental principles which are necessary for adequate maternal and infant care?

We believe that preconceptional care is basic, and in using this term I should like to stress the point that preconceptional care is a preparation for conception and for reproduction. In discussing preconceptional care we cannot avoid a consideration of both eugenic and eutheic viewpoints. This type of care is not only maternal but also paternal. In fact, it is both parental and ancestral. Proper reproduction may not be so vital for the individual, but it is paramount for the survival and success of the human race. We have much to learn about heredity, especially of its application to the human being. We must move slowly but surely in applying the laws of heredity to the control of human reproduction, but certainly where the parents, particularly the mother, offer both a bad heredity and poor environment to the progeny, some method of artificial selection and control would seem advisable. Hereditary factors should receive proper consideration in evaluating the ultimate outcome of a future conception. The proper preparation for future propagation begins at or before birth as the health of future parents influences that of the progeny.

The prevention of diseases which interfere with skeletal and other tissue growth and with development of the infant and child's body and brain is essential.

The prophylactic measures which minimize the incidence and seriousness of organ and tissue damaging infectious diseases must be universally applied, not only to maintain the health of the individual but also in the interest of the future family and community.

Adolescence arrives with its accompanying phenomena and problems of which both the individual, the family and the community should have a sane appreciation. There must have been both antecedent education and character building of the maturing persons thus enabling them to withstand the biologic shock of this rapidly developing aspect of life. Habit forming of various kinds is to be avoided, especially the various forms of drug habits which are often detrimental to the individual and may be harmful to germ plasm. Illicit relations and pregnancies constitute important biologic and social problems which no generation has yet solved satisfactorily. Sane biologic education, character building, and the establishment of proper family ties seem to offer the best approach for the solving of this biologic equation. These matters are closely related to venereal disease control, the solution of which health problem is being vigorously attacked from many angles, one of which is that of maternal care.

This brings us to a most important phase of preconceptional care, the necessity of which has long been recognized by some in order to safeguard the health and lives of the coming generation. Premarital examination is an answer to many questions which arise in the minds of individuals contemplating marriage. Intelligent and careful examination and advice to these young persons will avoid many a contagion, some of which might damage or kill a future baby, and prevent the development of unhappy families and their possible disruption.

The prospective family will be safeguarded medically, economically, and sociologically. Legislation alone, even with attempts at enforcement, will not be completely successful without intelligent and wholehearted cooperation of both professional and lay groups. There must be a good understanding of the underlying principles and objectives and of the benefits to be derived. Many unhappy lives and homes can be avoided by these relatively simple medical and social preventive measures.

It is necessary to recognize that successful medical and nursing care in general as well as that of mothers and babies is dependent upon many factors, such as facilities available, and upon economic and sociologic status. Nutrition may for instance be of the greatest significance from the standpoint of maternal care, but doctors and nurses cannot furnish the actual foodstuffs. There are many elements which are fundamental for the good health of all and particularly for that of mothers and babies. Many conditions affecting the individual and the community are beyond the control of the professional groups here represented. We cannot build houses, furnish clothes, or supply the things necessary for proper personal and community nutrition and hygiene. All of these are basic for the care of mothers

the head is born; this can usually be obviated. Warmth from the moment of birth is necessary for all but is vital for premature infants. Prevention of infection of the cord, the eyes, the skin, the gastro-intestinal tract, the nasopharynx, and the lower respiratory passages is necessary. Fluid and food, preferably breast milk, are, of course, essential. We have here considered particularly neonatal care as a phase of infant welfare which should go on with the thought that biologic principles govern the future of man.

In conclusion, it must be stressed that the care of mothers and babies should be a continuous process, each step leading inevitably to the next. The problem is greater than doctors and nurses alone can solve. It will require the cooperative effort of doctors, nurses, health workers, educators, scientists, administrators, sociologists, publicists, and the public to solve the problems surrounding human reproduction. Both private and public funds will be required to solve the problems and to carry on generally and successfully the necessary programs for the proper care of mothers and babies.

The practicing physicians, the nurses, the educators, the hospital administrators, and the public and the voluntary health workers who have assembled here at this Congress, the first of its kind, have by their effort, interest, and enthusiasm inaugurated this new cooperative movement which will bring us closer to our goal. I might outline the situation, now, as we end our meeting, in a few words:

1. Preconceptional care consists of the eugenic and euthenic preparation for marriage and reproduction. It includes proper growth and development from the beginning of life to maturity in all its phases. It is an essential factor in the elimination of disease and in the continuation and improvement of the human race.

2. Prenatal care is the attention given to the pregnant woman to maintain an optimum of health and comfort and to secure proper evolution of the pregnancy and development of the infant. This is accomplished by periodic evaluation of her health status for the early recognition of abnormal conditions, coupled with any necessary treatment, preventive or curative. It concludes with the necessary steps in the preparation for labor.

3. Intra-partum or delivery care, whether at home or in a hospital, requires the necessary physical setup, the essential equipment and trained personnel capable of giving competent maternal and neonatal care. It is vital that everything necessary to carry on routine care and to meet emergencies be available. It is not enough merely to save the mother's life, or to save the fetus; it is necessary to save both, and to leave them finally in a state in which they will ultimately be able to lead normal lives in the family and in society.

4. For the mother post-partum care is the next phase. It requires a period of rest and both medical and nursing attention. The mother must have proper hygiene and good nutrition. It is a period of recuperation and adjustment, during which essential routine care must be given and complications avoided or treated. The mother should be restored to normalcy with a desire and capacity for childbearing at the appropriate time, as well as being able to nurse and care for her infant.

Post-partum care should continue as a periodic supervision to maintain health, and to detect and treat any disease. Cooperation between the mother and her medical adviser is essential throughout life if serious illness is to be prevented or detected early enough to avoid serious consequences.

5. For the baby the postnatal care includes the immediate neonatal care and the more remote infant care. The baby should be examined promptly for any abnormalities and be supervised during early infancy and later life. Delicate adjustments are occurring during neonatal life and careful and capable attention is essential to maintain growth and development and to detect and treat variations from the normal.

It is to promote the best interests of mothers and their newborn babies that this Congress has been held. The solution of the varied problems involved in this objective is a task both national and local in scope, and it is only through understanding and cooperation of all agencies and individuals interested in these programs that progress can be made.

The sequence of intra-partum care follows with the onset of labor whether it is premature, at term, or postmature. The necessity for artificial stimulation of the onset of labor sometimes arises, but unless this coincides with the preparatory phase occurring at the end of gestation, an abnormal course of labor is likely to ensue. The conduct of labor requires great judgment and care and the paramount consideration is, of course, the safety of both mother and baby. One may seem to be hard and callous at times in not yielding to the pleadings of patients and friends for relief or for a speedy termination of labor, but one has to be kindly sympathetic but never soft. One cannot allow sentiment to overcome good judgment.

There is much said about radicalism and conservatism in obstetric practice. We should understand what these terms mean. Operative procedures are a part of our treatment. Medicaments are part of our armamentarium. The same drug, as for example pituitary extract or ergonovine, may be used radically or conservatively. By this I mean that in the one instance it may produce a casualty and in the other it may save a life. As an illustration, these agents used radically during labor may provoke a uterine rupture or cause a fetal death. When used rationally and conservatively their use may save a woman from post-partum hemorrhage.

The same statement applies to treatment by a surgical procedure which of itself is not radical as it is designed to be life saving. Operations become radical when not justified or indicated and when the personnel and environment are not suitable. A cesarean section may be conservative and life saving under one set of circumstances and irrational and radical in a different situation. The same statement applies to other surgical procedures. Even as relatively simple a procedure as the repair of a laceration, ordinarily considered conservative, might be radical under some circumstances.

Radicalism or conservatism is then based upon the result so far as the future life and health of the patient is concerned and not upon the procedure itself, provided, of course, the method is sound.

The completion of the three so-called stages of labor is followed by the dual problem of post-partum and postnatal care. Both begin immediately, and at times a limited number of attendants may need to extend their ability and energy to the limit to give the proper care to both mother and baby. These emergencies cannot always be foreseen and constitute one potent argument for institutional care where adequate equipment and personnel should be available.

For the mother the post-partum phase is a crucial period as she must recover from the analgesia or anesthesia, be protected from hemorrhage and possible infection, and have injuries repaired. The immediate crucial period is over and the lying-in period follows with the involutional processes going on, the breasts beginning to function and her normal health and vigor being re-established. Her subsequent life should be governed and supervised by her own good sense and that of her advisers who should be intelligently selected. Follow-up examinations are necessary at intervals and unusual signs or symptoms should always throughout her remaining life lead her to find the cause by securing careful and intelligent examination and advice. Every woman as well as man is exposed to the possible development of some disease which cannot be prevented by our present knowledge. Many of these may be remedied by early detection and treatment or their course favorably modified. Cancer is one of these diseases. The means of prevention are unknown unless susceptibility can be bred out of the human race. Cure is possible, but this depends almost entirely upon early detection and treatment. Time is too limited to even mention other conditions which with our present knowledge cannot be prevented or be cured. Attention to the occurrence of any unusual or unexplained symptoms is necessary if the serious consequences of tuberculosis, of heart, and vascular or renal disease and of malignancy are to be avoided.

No one can replace a mother in the interest in her baby, and though intuition and maternal instinct are of great importance, they must be supplemented. Mental attitude, proper training and education, the time, the opportunity and the resources are essential for proper motherhood and postnatal care. This care begins almost before the process of birth is completed. The prevention of injury and suffocation during labor are not always avoidable. The baby may aspirate material as soon as



# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### Pregnancy and Disease

*(Continued from September issue.)*

Houel, J. E.: Acute Obstetrical Postoperative Parotitis, Bull. Soc. d'obst. et de gynec. 27: 231, 1938.

There is a great affinity between the salivary glands, especially the parotid glands and the genital glands. This explains the great frequency with which disturbances in the parotid glands occur in women because in them, interventions on the genitalia are frequent. Thus among 100 cases of postoperative parotitis, 75 will be in women and only 25 in men. In spite of this frequency among women, Houel has been able to find only seven cases of postoperative obstetric parotitis including one of his own. All of these cases occurred in women who had serious dystocia and prolonged labors which required operative intervention. Five of the women had cervical cesarean sections and 2 had been delivered by forceps. In not one of the cases was there a puerperal infection.

The treatment consists of catheterization of Stenson's canal. If this is not sufficient, surgical treatment must be used.

J. P. GREENHILL.

Sheehan, H. L., and Murdoch, R.: Post-Partum Necrosis of the Anterior Pituitary, Lancet 1: 132, 1938.

Massive necrosis of the anterior pituitary gland is a relatively frequent finding in patients who die during the puerperium after a delivery complicated by collapse or severe hemorrhage. Patients who survive may develop a clinical syndrome, the main symptoms of which are absence or scantiness of the menses, asthenia, hypothermia, apathy, and sometimes weight loss.

In 54 cases investigated by the authors, there was no subsequent improvement in 12 cases showing genital atrophy. In the remaining 42, some recovery occurred in the majority. In 3 there was complete spontaneous recovery without specific therapy. There is nearly always a marked recovery if the patient becomes pregnant again. This usually appears early in the pregnancy and is permanent unless hemorrhage or shock is associated with the delivery. Occasional cases show no improvement as a result of pregnancy.

Case reports are given which show the improvement with subsequent pregnancy and illustrate the danger of relapse or even death from hemorrhage or collapse at delivery.

CARL P. HUBER.

Mortara, F.: Contribution to the Study of Nervous Diseases in Pregnancy, Myasthenia Gravis Pseudo Paralytica, Riv. ital. di ginec. 21: 369, 1938.

The author feels that in a pregnancy complicated by a myasthenia gravis, interruption is almost always indicated. The medical management is rather difficult although symptomatic benefit may sometimes be had with the use of prostigmine.

MARIO A. CASTALLO.

The health and lives of mothers and babies are most necessary for the integrity of the family and the welfare of the community. In a broad sense our problem is both biologic and sociologic, and it cannot be solved in the face of conflict between these fundamental sciences but only by a proper and cooperative understanding and effort.

The program of safeguarding these lives is much broader than its medical and nursing aspects. It has ethical, economic, and sociologic bases which can only be established and built upon safely by proper evaluation of all the factors and by cooperation among all those elements in the community which can be enlisted in the fight to save rather than destroy life. The enlistment is for the duration of this, our war.

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## Society Transactions

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### NEW YORK OBSTETRICAL SOCIETY

*MEETING OF MARCH 14, 1939*

The following papers were presented:

**Transvesicle Repair of a Vesicovaginal Fistula.** Dr. Henry T. Burns.

**Current Views on the Causation of Menstruation.** Dr. Earl T. Engle (by invitation). (For original article, see page 600.)

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### CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF FEBRUARY 17, 1939*

The following papers were presented:

**The Uterus Arcuatus.** Dr. Frederick Falls. (For original article, see page 661.)

**Indirect External Hysterography.** Drs. Con Fenning (by invitation), M. Edward Davis and Fred L. Adair. (For original article, see page 670.)

**Suburethral Abscesses, Urine Pockets and Diverticula in the Female Urethra.** Drs. Herbert E. Schmitz and Peter A. Nelson (by invitation). (For original article, see page 707.)

**Hydrocephalus and Spina Bifida Diagnosed by Roentgen Examination Before Labor.** Dr. J. B. DeLee.

*MEETING OF APRIL 21, 1939*

The following papers and case reports were presented:

**Prolapse of the Uterus, Hydronephrosis, Hypertension.** Dr. Paul H. Wosika (by invitation) and Dr. Chauncey C. Maher (by invitation). (For original article, see page 684.)

**Strictures of the Cervix.** Dr. Hilliard E. Miller (by invitation) and Dr. E. Perry Thomas (by invitation).

**Vaginal Removal of Repeated Ectopic Pregnancy.** Dr. E. Allen. (For original article, see page 717.)

**Reconstruction of a Bicornate Uterus Followed by Two Full-Term Pregnancies.** Dr. A. E. Kanter.

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### PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

*MEETING OF APRIL 4, 1939*

The following papers were presented:

**Extra- and Intrauterine Pregnancy.** Dr. David B. Ludwig.

**Two Cases of Bicornate Uterus Associated with Pregnancy.** Dr. James W. Stevenson.

"is at this time in satisfactory condition," with a reduction in the size of the lesion following x-ray therapy. He is not specific concerning the patient's status, the length of time she has been under observation, or the details of her treatment.

A second patient, aged 33 years, gravida xii, had her last child 14 months previously. At two and a half months the present pregnancy was complicated by vaginal bleeding. The portio vaginalis of the cervix was found to be distorted by an ulcerating crater which bled readily. Under spinal anesthesia a Wertheim operation was performed with an uneventful postoperative course and primary healing. Two months after operation the patient's general and local condition was good.

ARNOLD GOLDBERGER.

King, Faust and Sanders: Intestinal Parasitic Infections Complicating Pregnancy, South. M. J. 30: 545, 1937.

During 6½ years, stool examinations were made on 3,290 white obstetric patients; in some instances, two or three specimens from the same patients were examined, so that over 5,000 careful examinations were made.

From an obstetric point of view, it is apparent that clinical amebiasis, especially if severe, might be serious complication. None of the patients presented serious symptoms, though in approximately one-half of them the presence of diarrhea or dysentery of variable intensity was noted. The authors agree with Craig that all individuals with amebic infection should be treated, and they see no objection to, and many reasons for, the treatment of pregnant women so infected. The authors know that their general health would be improved and they would not expect the occurrence of abortion or of premature labor as a result of the treatment. However, they were not able to treat many of the patients, owing to the fact that the large majority were in the ward for only a few days. It might be noted that the drugs most favored in management of this condition are chiniform, carbarsone and vioform.

Hookworm infection was found in 185 patients (5.6 per cent). It is apparent that a woman with this disease is handicapped to a degree corresponding to the intensity of the infection. This is due in great part to the anemia commonly found, with the concomitant lowering of resistance.

The authors had no case of abortion or premature labor as a result of treatment; on the contrary, they feel that such a termination is often avoided because of the improved condition of the patient following eradication of the infection. They prefer the use of tetrachlorethylene in 3 c.c. doses given in hard gelatin capsules on an empty stomach; a saline purge is given the night before and again two hours after administration of the drug. If ascaris is also present, hexylresorcinol is given at the same time. It is as necessary to treat the anemia as to eradicate the infection, and obviously this is particularly true in pregnancy.

J. P. GREENHILL.

Bolaffi, R.: Spontaneous Fracture During Pregnancy, Gynecologia 15: 593, 1937.

The author describes a case of spontaneous fracture of the maternal pelvis, without apparent cause, in a primipara seven months pregnant who was slowly walking in the street. Pregnancy proceeded normally and the healing process of the fracture studied by x-ray was normal. The delivery of a 3,350 gm. living fetus was also normal. The author emphasizes the rarity of this observation.

AUGUST F. DARO.

Szendi, B.: Morphologic and Biologic Changes Caused by *Trichomonas Vaginalis* in the Vagina of Pregnant Women, Arch. f. Gynäk. 162: 479, 1937.

*Trichomonas vaginalis* was found in the vagina of 44 per cent of the 200 women studied. There were no symptoms in about one-third, one-third showed a foamy discharge and the remaining group (30 per cent) had a definite vulvovaginitis with

Zambonino, F., and Martines, S.: Report of a Case of Posterior Hypophysitis in a Pregnant Woman Characterized by an Infective Toxic Psychosis, *Riv. ital. di ginec.* 20: 193, 1938.

The authors present a fatal case of posterior hypophysitis in a pregnancy of eight months with symptoms of psychosis and hemorrhagic nephritis. They describe in full the clinical and histoanatomic picture.

AUGUST F. DARO.

Sheehan, H. L., and Murdoch, R.: Postpartum Necrosis of the Anterior Pituitary, *Lancet* 1: 818, 1939.

In a previous study the authors have pointed out that patients with an anterior pituitary insufficiency due to a postpartum necrosis of this gland can be cured symptomatically by a subsequent pregnancy provided that there are no serious complications at the delivery. They now report the successful treatment of such a patient in whom complete amenorrhea, menopausal symptoms, hyperinvolution of the uterus and increasing vaginal atrophy had been present since her fourth pregnancy at age 29.

The successful treatment was begun four and one-half years after the onset of symptoms. It consisted of the following over a period of 37 days: Days 1-37, progynon B in oil 50,000 I.B.U. every 2 days; days 21-37, proluton 5 mg. every 2 days; days 26-32, antex leo 100 mouse units daily (7 times). Bleeding occurred on the 31st day of therapy and continued for two weeks. Pregnancy was calculated to have begun 6 weeks after the course of treatment. Normal delivery resulted. The authors believe that the most probable explanation is that the extract of pregnant mare serum (antex leo) stimulated the development of follicles in the ovaries; that the resultant production of estrin maintained the hypertrophy of the genital tract previously produced by the injected estrin (progynon B); and the rupture of one of the artificially stimulated follicles liberated an ovum.

CARL P. HUBER.

Stern, S. I.: Pregnancy at Term and Cancer of the Cervix, *Gynéc. et obst.* 37: 295, 1938.

Pregnancy at term with coincident cancer of the cervix is rare. In nine years it was encountered only once among 14,000 births. Special interest is attached to this case report because it describes the spontaneous birth of a normal infant.

The patient, aged 38 years, para i, gravida ii, with a gestation approaching term came to prenatal clinic complaining of a foul, bloody, irritating discharge. Her previous gestation nine years ago had a spontaneous termination. On the posterior cervical lip and spreading to the vaginal vault there was a friable, exophytic tumor mass, 6 to 7 cm. in diameter, which bled on slight manipulation.

Approximately eleven hours after onset of labor the membranes ruptured. Cesarean section was planned, but a preliminary vaginal examination revealed complete cervical dilatation with the baby's head in the vagina. A 3,300 gm. male infant was born spontaneously. The amniotic fluid had a foul odor and a greenish tinge. No difficulty was encountered in the delivery of the placenta and the total blood loss was moderate. Though somewhat slow, the mechanism of labor was essentially normal and of a total duration of 16 hours. Except for some temperature elevation (37.2° to 38.3° C.) until the fifth day, the puerperium was uneventful. Uterine involution was normal. Speculum examination at the time of discharge revealed no change in the gross appearance of the tumor.

Histologic diagnosis of the cervical lesion was "basal cell cancer"; of the placenta, "hyalinization with placentitis."

The favorable course of labor and its uncomplicated termination was attributed to the fact that the tumor mass did not penetrate deeply into the cervix. Despite the size of the baby no cervical tear resulted, and in the presence of a large focus of infection puerperal sepsis did not occur. The author reports that the patient

## Correspondence

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*To the Editor:*

In the February, 1939, issue of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* Dr. E. W. Page discussed the relationship between hydatidiform moles, ischemia of the gravid uterus, and the placental origin of eclampsia. He mentioned the well-known association of moles and toxemia and from that expressed a postulation. In my own words, he reasoned that some gravid uteri cannot supply enough blood to nourish the growing products of conception; hence there comes a time when growth overcomes blood supply and ischemia occurs in the uterus and placenta. This effect in the placenta causes the production of pressor substances which are excreted into the maternal blood system by the placenta, as a mechanism to increase the maternal blood pressure which in turn increases the uterine blood supply for the placental growth. From this increased blood pressure the pre-eclampsias get their start.

This reasoning presents a fallacy which should not be left without comment. Suppose in such an individual woman the stage has just arrived when the total uterine blood supply (designated as A amount) just satisfies the growing products of gestation. The bulk of these products we will call X amount. From now on he reasons that the A blood supply will fall behind the X bulk growth. Soon bulk X will increase to bulk X plus Y with the same A amount of blood. Just where does this new bulk Y get its protein, carbohydrates, hormone, and vitamin supply to form this new mass of tissue Y? It cannot get it from the uterine supply A which can only supply the bulk X.

Basically the fallacy of this reasoning lies in the fact that the author assumes that from the time of conception the fertilized ovum has the inherent power of growth regardless of food supply. To make it sound ridiculous, let us say, cut off all the blood and lymph supply to the uterus and still the products of gestation will continue to grow.

Food supply is the basis of growth without which no tissue will grow. Hyperplasia at the expense of bulk might occur but new bulk cannot be created without new molecules supplied to it. If blood A just satisfies bulk X the products of conception will stop further growth in the sense of increased mass. In my belief, there is no reason for assuming that uterine ischemia depends upon independent placental growth.

GEORGE F. PENDLETON, M.D.

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*Reply by Dr. E. W. Page*

*To the Editor:*

Dr. Pendleton has quite properly raised the much discussed question as to the relation between growth and blood supply. Recent experiments by Drury (*J. Exper. Med.* 68: 693, 1938) have shown that, when the blood supply to the kidney of a young rabbit is limited, that kidney will continue to grow until an equilibrium is reached and then growth is stopped. Not only will the excretory function of that kidney continue to be normal, but its "demand" for blood is greater than its supply, and it is able to effect severe hypertension through a humoral mechanism, presumably by the liberation of a pressor substance. Should the blood supply to the gravid uterus similarly be limited, the rate of growth would, as Dr. Pendleton suggests, undoubtedly be retarded and eventually stopped. It is my contention that when this equilibrium is reached the placenta, like the kidney, is capable of effecting hypertension through some humoral mechanism. Whether the placenta or fetus continues to increase in size during the acute hypertensive phase of late toxemias would obviously be very difficult to determine clinically.

inflammatory changes. The discharge is caused by an acute suppurating inflammatory reaction in the vaginal mucosa with vesicle and pustule formation. It is often characterized by a moldlike pseudomembranous coating followed by superficial ulcerations and an infiltration of the epithelial and subepithelial layers. The glycogen content of the vaginal mucosa is always greatly reduced. The trichomonas is never found in the tissue itself but lives on the cast-off debris. It lives in symbiosis with the bacillus of Doederlein and produces lactic acid. This accounts for the fact that the changes are relatively mild and also for the fact that many authors deny the pathogenicity of the trichomonas. This production of lactic acid actually inhibits the growth of other organisms even though the pathology produced makes the entrance of pathogenic bacteria easier. The trichomonas plays no role in the production of puerperal morbidity.

RALPH A. REIS.

Farias, L. L.: Appendicitis in Pregnancy, *Bol. Soc. Chilena de obst. y ginec.* 2: 171, 1937.

The author reports 13 cases of appendicitis complicating pregnancy observed in 1,129 pregnancies.

There were three deaths in this group: all had generalized peritonitis. Of the remaining 10, all went to term except one. The pregnancies were advanced from two to seven months when operation was performed.

MARIO A. CASTALLO.

Geschickter, Charles F., and Lewis, Dean: Pregnancy and Lactation Changes in Fibro-Adenoma of the Breast, *Brit. M. J.* 1: 499, 1938.

Fibroadenomas of the breast are firm, slow-growing encapsulated growths and usually give little trouble in diagnosis. However, during pregnancy and lactation they change so markedly that confusion in diagnosis often results and mutilating operations may be done unnecessarily.

A series of fibroadenomas is reported, representing every phase of pregnancy, lactation, and poor lactation involution. The changes occurring in this series are correlated with those produced experimentally in the breasts of human beings and other mammals by the injection of the various sex hormones.

The growth of mammary ducts and periductal fibrous tissue in both animals and human beings is stimulated by estrin. The histology of fibroadenomas removed at puberty, characterized by growth of ducts and stroma without evidence of lobule formation, suggests that these neoplasms represent an increased response to estrin on the part of the tissue involved. Estrin is present in increased amounts also during the first trimester of pregnancy. At this period there is a rapid growth of fibroadenomas.

Advanced fibrosis, with hyalinization or myxomatous changes in the stroma of a fibroadenoma of long standing or in tumors with an unusual intensity of estrogenic response, accounts for those fibroadenomas which remain refractory to the hormonal influences of pregnancy and lactation.

During lactation these tumors involute and often secrete, resulting in cyst formation. This change can be stimulated by the lactogenic hormone of the anterior lobe of the pituitary gland. In general, the lactogenic hormone seems to hasten and make more marked involutional changes.

F. L. ADAIR AND JOHN A. HAUGEN.

than November 15, 1939. Candidates who are required to take reexaminations must do so before the expiration of three years from the date of their original examination.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J., on June 8, 9, 10, and 11, 1940, immediately prior to the annual meeting of the American Medical Association in New York City.

Application for admission to Group A, Part II examinations must be on file in the Secretary's Office not later than March 15, 1940.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

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## Books Received

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**LAS INCRECIONES DEL OVARIO.** Par Carlos Colmeira Laforet, La Coruna. Liberia "Gali." Santiago de Compostela, Spain. 1939.

**THE ENDOCRINE GLANDS.** By Max A. Goldzieher, Endocrinologist, Gouverneur Hospital and Brooklyn Women's Hospital, New York, etc. Illustrated with 271 figures, 916 pages. D. Appleton-Century Company, New York, 1939.

**PRIESTS OF LUCINA.** The Story of Obstetrics. By Palmer Findley, M.D. Illustrated, 421 pages. Little, Brown & Company, Boston, 1939.

**WHAT IT MEANS TO BE A DOCTOR.** By Dwight Anderson. Public Relations Bureau, Medical Society of the State of New York, New York, 1939.

**A HANDBOOK OF ELEMENTARY PSYCHOBIOLOGY AND PSYCHIATRY.** By Edward G. Billings, M.D., Assistant Professor of Psychiatry, University of Colorado School of Medicine, etc. The Macmillan Company, New York, 1939.

**STERILITY AND IMPAIRED FERTILITY.** By Cedric Lane-Roberts, Gynecological Surgeon, Royal Northern Hospital; Albert Sharman, Assistant Surgeon, Royal Samarital Hospital in Glasgow; Kenneth Walker, Surgeon to Genito-Urinary Department, Royal Northern Hospital; and B. P. Wiesner, Consulting Biologist, Royal Northern Hospital. Illustrated, 419 pages. Paul B. Hoeber Inc., New York, 1939.

**MATERNAL CARE AND SOME COMPLICATIONS.** Edited by Dr. F. L. Adair, approved by American Committee on Maternal Welfare, Inc. University of Chicago Press, Chicago, 1939.

**DIE GONORRHOEE DER FRAU.** Von Dr. Karlheinz Sommer, Marinestabsarzt, Universitaets Frauenklinik in Leipzig. Mit 47 Abbildungen, 185 Seiten. Verlag von Georg Thieme, Leipzig, 1939.

**WACHSTUM, GESCHLECHT UND FORTPFLANZUNG,** als ganzheitliches, erbmaessig-hormonales Problem. Von Professor Dr. Ludwig Seitz. With 125 illustrations including color plates, 410 pages. Verlag von Julius Springer, Berlin, 1939.

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## Erratum

In the article "Studies on the Concentrations of Estrogenic and Gonadotropic Hormones in the Serum of Pregnant Women" by Dr. A. E. Rakoff in the September issue of the JOURNAL, the second paragraph of the legend under Fig. 1, page 373, beginning "In further studies in early pregnancy, etc." should appear with the legend for Fig. 2, page 374. This correction has been made in the author's reprints.

Actual proof of this concept must, of course, rest in the laboratory. We have, in a series of unpublished experiments, limited the blood supply to the gravid uteri of dogs by partial constriction of the aorta below the renal vessels and have observed a gradual rise of blood pressure beginning within twenty minutes and eventually reaching a considerable height. After release of the clamp, the blood pressure will return to its basal level. This rise of blood pressure is not obtained after removal of the pregnant uterus, nor in a nonpregnant dog, and must therefore be accomplished through some humoral mechanism. This phenomenon has never been described before, and much work is needed, of course, to elucidate its mechanism. The results to date, however, are quite in accord with my theory of etiology of eclamptic hypertension.

ERNEST W. PAGE, M.D.

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## Items

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### Directory of Medical Specialists

The Advisory Board for Medical Specialties will issue in December the first edition of the Directory of Medical Specialists listing the more than 16,000 specialists certified to date by the twelve American Boards and the two affiliate Boards in the Specialties.

This Directory will have three sections. The first will be devoted to a brief discussion of the Advisory Board for Medical Specialties, its organization and objectives. The second section will have fourteen separate divisions, one for each American Board with a geographic and a detail biographic listing of its Diplomates. Each of these divisions will give full information regarding requirements for admission to examinations for certification, details of organization of each Board, and other general information. The third and final section will be a complete alphabetic list of all the 16,000 Diplomates, with their addresses and indications of specialty certification.

It is expected to issue the Directory every two years. No charge is made for any listing in the Directory, and only the names of the specialists certified by the American Boards will be included.

It represents an effort officially to inform the lay and medical public regarding the present strong movement for certification of qualified medical specialists, and is expected to have wide use as a reference work in this respect.

The Directory should be invaluable to the entire medical profession in the reference of patients, as well as in many other ways, and the individual support of this new project of the American Boards is earnestly solicited.

The Directory will be sold generally to physicians, libraries, hospitals, and others by subscription. Such subscriptions at \$3.50 per copy, may be made through the Columbia Press, 2960 Broadway, New York, N. Y., or through the office of the Directing Editor, Dr. Paul Titus, 1015 Highland Bldg., Pittsburgh, Pa.

### American Board of Obstetrics and Gynecology

The written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 6, 1940, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held in June, 1940.

Candidates for reexamination in Part I (written paper and submission of case histories) must request such reexamination by writing the Secretary's Office not later



ephemeral value. For instance, the extirpation of functionally active ovaries, the attention paid to uterine flexures and to stenosis of the cervix—these and many others have very little significance now, but were the subject of mighty battles in their day. It would seem worth while to attempt to evaluate those contributions which record actual advances, contributions which have stood the acid test of time, and which will engage the attention of historians of our specialty for centuries to come.

In the first volume of the transactions, we find Emil Noeggerath's classic contribution "Latent Gonorrhoea, Especially With Regard to Its Influence on Fertility in Women." He set forth startling views which met with great opposition in the ensuing discussion. In closing, the author stated that "after the gentlemen have given five years or more of careful study to this question I shall expect to hear more approval than I have done today." Three years later Neisser isolated the gonococcus.

In 1878, Thomas Addis Emmet contributed a paper on "The Necessity for Early Delivery, as Demonstrated by the Analysis of One Hundred and Sixty-One Cases of Vesico-Vaginal Fistulac." Appearing ten years after his great book on vesicovaginal fistulas, this paper represented his mature views as to the cause of this tragic injury. He pointed out that instrumental delivery was rarely, if ever, the agent in the production of vesicovaginal fistula, but that the direct cause was always delay in delivery. Not "meddlesome midwifery," but delay in the use of forceps was the important factor.

When we remember that the Woman's Hospital in New York was organized and established for the purpose of the cure of vesicovaginal fistula caused by obstetric trauma, we well realize how important a contribution was made by Sims and Emmet to the advance of obstetrics and the great reduction of the incidence of this calamity.

The introduction of anesthesia in 1846 had robbed surgery of its terror. Three great dangers of surgery still remained: shock, hemorrhage, and infection. The year this society was founded was marked by the meeting of the International Medical Congress at Philadelphia. The great Lister himself was present at this meeting and entered into the discussion of the problem of infection. According to Lusk, the views of Lister were received by a curious but unsympathetic audience. The majority of medical men still clung to the idea of spontaneous generation and scoffed at the germ theory of disease.

Not until 1883 was a paper read before the Society applying the ideas of Lister to gynecology. R. Stansbury Sutton read a paper on "Cleanliness in Surgery." The author had a very clear insight of the importance of asepsis implicit in Lister's teaching, while Lusk in the discussion, paid tribute to Lister's great contribution. Albert H. Smith, however, in his presidential address the following year, discussing the etiology of puerperal infection, denied the doctrine of its germ origin. While this debate was going on, three members of the society were proving for the first time in America that the application of asepsis and antisepsis could reduce the dreadfully high mortality in our lying-in institutions. Garrigues, at the Charity Hospital, New York, Lusk, at the

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American Gynecological Society

Sixty-Fourth Annual Meeting, May 22, 23, and 24, 1939

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## PRESIDENTIAL ADDRESS\*

FREDERICK C. HOLDEN, M.D., NEW YORK, N. Y.

FORTY-SEVEN years ago I attended my first meeting of the American Gynecological Society, and recently browsed through the sixty odd volumes of the Transactions. I should like to present a few examples of the great debt which the Society owes to some of its members; to compare briefly its present activities with those of the early days; and last, to discuss certain present-day trends.

The medical historian, J. H. Bass (*Outline of the History of Medicine*, 1889) wrote that gynecology is a specialty "in which American medicine has won, perhaps, its most enduring laurels." Prior to 1850, gynecologic surgery did not exist. In 1876, however, when the most prominent gynecologists from various parts of the United States came together to form the American Gynecological Society, the specialty was already firmly established. In the short space of a quarter of a century, a brilliant and rapid advance had taken place in which the founders of this society played an important role. Well might Fordyce Barker assert in the first presidential address that "in obstetrics and gynecology, the progress in science and its resultant improvement in practice have been greater during the past one hundred years than the whole advance made during the previous ten centuries."

" 'Tis opportune to look back upon old times, and contemplate our forefathers" wrote the learned Sir Thomas Browne. The achievements of Atlee, Sims, Emmet, Peaslee, Goodell and Parvin are an inspiration for all succeeding generations. It is true that many contributions which seemed highly significant a half century ago have proved of

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\*Read at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

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NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

I have recalled to your attention a few of the outstanding contributions of our Fellows which appeared over the space of sixty years. If time permitted, the list could be lengthened considerably. In the operative treatment of fibroids and of prolapse, in the introduction of radiation therapy for cancer and other pathology, in every aspect of gynecology, important work has been done by members of this society.

Of great importance has been the union of gynecology and obstetrics. This was not brought about without a struggle. Theophilus Parvin devoted his presidential address in 1893 to the necessity of the fusion of these two scientific branches. As a supplement to his address, a paper was read by F. Winckel of Munich on "The Necessity of the Union of Obstetrics and Gynecology as Branches of Medical Instruction." Few today would deny their conclusion that progress in obstetrics goes hand-in-hand with progress in gynecology; the one advances the other.

Lusk, fourteen years prior to this time had stated before the Society that he had "nothing but words of praise and honor for those who have contributed so much in the past ten years to perfect the practice of gynecology." He regretted however that "the flattering interest their labors have excited has tended to weaken interest in the sister department of obstetrics. While our young men seem all desirous to make a specialty of the diseases of women, it is hard to obtain a hearing for the statement of the very trite fact that it is midwifery which gives to gynecology nearly all its importance."

In reviewing the history of our specialty, one is bound to compare the program of the first meeting of this Society with that of today. What were some of the presentations in 1876? Forty-six pages about uterine flexures and forty-eight pages about the knee-chest position under the title "Pneumatic Displacement in Dislocation of the Gravid and Non-Gravid Uterus." Extirpation of functionally active normal ovaries in young women as a remedy for a variety of diseases; tumors; obstetric injuries amongst which vesicovaginal fistula was a frequent occurrence, and Noeggerath's paper which has stood the test of time "Latent Gonorrhea With Regard to Its Influence on Fertility in Women."

Spanning the years to today's meeting, what an inspiring vista we have: Increasing accuracy of diagnosis; asepsis and antisepsis with their tremendous influence; the rapid improvement in surgical technique; the progress in anesthesia and in preoperative and postoperative care; the microscope with its influence on pathology and bacteriology; radiotherapy; and always increasingly in evidence, the continuous advancement of medicine into the realm of pure science particularly in endocrinology. There has likewise been commendable advance in the teaching and training of our doctors. On the other hand there is intensive training of a small group of experts. Of equal importance is the better training of the general practitioners, particularly in the field of obstetrics, by planned postgraduate lectures, and hospital guidance, as carried out by the policy of an open courtesy visiting staff in some of the leading obstetrical hospitals.

As we glance over today's program, clinical medicine is in the background while scientific investigation, especially in that fascinating field of endocrinology, comes more and more to the foreground.

Emergency Hospital and Richardson at the Boston Lying-In, were proving by their results that Lister and Pasteur were right, and those who scoffed at germs were wrong.

In 1887, William M. Polk laid the foundation of conservative gynecological work in this country in a paper entitled "Are the Tubes and Ovaries to Be Sacrificed in All Cases of Salpingitis?" He shares honor with C. Schröder and A. Martin of Germany for his demonstration of the possibility of restoring function in diseased adherent tubes and ovaries and of the functional value of amputated and opened tubes.

Polk returned to this subject again in 1893 in an article entitled "Operations Upon the Uterine Appendages With a View to Preserving the Functions of Ovulation and Menstruation." The paper created unusual discussion, and warm admiration was expressed for Doctor Polk's courage in taking a position on which he was liable to be attacked from all quarters.

Conservative surgery for pelvic inflammatory disease was further aided by the work of Frank F. Simpson. In 1909, he read a paper entitled "Choice of Time for Operation for Pelvic Inflammation of Tubal Origin." He showed that perhaps the majority of patients with pelvic inflammation have their organs restored practically to normal without operation. He pointed out the danger of operative interference during the acute stage and laid down the rules for the choice of time of operation. Simpson's rules are observed to this day.

John Whitridge Williams presented his work on "Tuberculosis of the Female Generative Organs" partly as a result of which he received the honor of Fellowship in this society when only twenty-six years of age. Three years later he again appeared before the society to present a paper of perhaps even greater importance in the domain of pelvic pathology, "Deciduoma Malignum." This contribution ranks with the important monograph of Marchand which appeared at this time, proving the fetal origin of chorionepithelioma, and was the beginning of an extensive literature on this subject.

In 1902, John T. Thompson, presented a paper on "Ovarian Pregnancy With Report of a Case," in which he demonstrated for the first time a conclusive specimen of ovarian pregnancy.

An epochal paper appeared in 1921 by John A. Sampson on "Perforating Hemorrhagic (Chocolate) Cysts of the Ovary." The following year he read a paper "The Life History of Ovarian Hematomas (Hemorrhagic Cysts) of Endometrial (Müllerian) type." This paper in which Sampson developed a new explanation for these hitherto inexplicable growths has been characterized by Robert T. Frank as of great fundamental importance.

Papers dealing with the more basic scientific aspects of our specialty appeared with increasing frequency in the later volumes of the Transactions. Illustrative of the new trend of interest in the physiology of the reproductive tract was the contribution of Robert T. Frank on "The Function of the Ovary" which appeared in 1911.

A paper which stimulated a great deal of discussion and had an enormous influence on obstetrical practice was that of Joseph B. DeLee in 1920, on "The Prophylactic Forceps Operation."

# THE RELATIONSHIP OF THE ESTROGENS AND OTHER PLACENTAL HORMONES TO SODIUM AND POTASSIUM BALANCE AT THE END OF PREGNANCY AND IN THE PUERPERIUM\*

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TWO distinct general conceptions of the nature and origin of the toxemias of pregnancy have guided recent research in two apparently quite divergent channels. In one direction are the endocrines, a very promising field, for it seems hardly possible that the substances which determine to such an extent the characteristic physiologic changes of pregnancy should not be in some sense responsible for a disease which occurs only in pregnancy. On the other hand are the physical and chemical phenomena of water and electrolyte exchange, which for the moment seem more closely related to the classical symptoms and signs of pre-eclamptic toxemia. Recent experiments showing that the estrogens and progesterone may cause the retention of sodium and of water suggest a line of investigation by which the hormonal and the physicochemical conceptions of toxemia may perhaps be reconciled.

The precise intention of this study has been to determine whether in pregnancy changes in the concentration of the estrogens and other placental hormones have any effect on the retention and excretion of sodium and potassium. The general method of investigation has been the measurement of the balance of sodium and potassium intake and output during alterations in the hormone content of the blood and the urine. The changes in hormone concentration made use of have been those occurring at parturition, after intrauterine death of the fetus and those following the intramuscular injection of estrogenic substances.

## THEORETICAL CONSIDERATIONS

Before proceeding to the report of the present study, it is necessary to mention certain previous clinical observations and experiments which appear to make important an investigation that is concerned with sodium and potassium, with the placental hormones and with the relationship between hormones and electrolytes.

1. Sodium. There is good reason to believe that sodium is one factor in the production of those symptoms or signs of toxemia which are dependent on the retention of fluid. This is the rationale for the low salt diet which forms such an important part of the currently popular dehydration therapy for pre-eclampsia. Two

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In our Society today, along this span between the old and the new, we have a group of eminent clinicians who would be unable to discuss many of the papers presented today, because of lack of knowledge. We have had difficulty in getting men to discuss some of today's papers, because the only ones who can discuss these papers are those who wrote them.

We see therefore the amazing progress from empirical medicine to the rapid and increasing advancement of the science of our specialty. Although we feel justifiable pride in this scientific progress, let us not lose sight of the fact that the art of medicine remains of equal importance. The art of medicine must continue to be taught, practiced, and its growth and development encouraged. Patients are human beings and not guinea pigs, and the ills of the human body cannot and must not be completely disassociated from the mental, emotional and psychic content of the individual we are treating.

Our world of today is becoming rapidly more complex. Great forces are at work, many of them capable of destroying all of our constructive efforts. Social programs of national scope affecting the health and well-being of our people are in the process of formulation.

We as a group, the individual members of which are recognized leaders in our respective communities, must assume our full responsibilities and accept our duties of leadership towards the direction that we think right. This means not only the teaching and practice of our specialty, it means not only scientific research, but today it also means taking an active part in formulating that part of the national health program which will be the deciding factor as to what kind of medical care will be given to our nation, and how it is to be administered. We can no longer retire to our clinics and laboratories, but must take our proper places in all broad programs of social welfare which affect the health of our people.

The early great physicians of this country because of their learning and leadership were looked to for advice in all the problems of the body politic. In order to carry through those principles which we think are essential for the preservation of freedom and scientific thinking, and the maintenance of the highest type of medical care, we must include in our program an awareness and participation in every angle of medical care and of its administration.

Our Society might properly be the consultation board for any legislation affecting particularly maternal welfare and any other public health program coming within the scope of either branch of our specialty. I strongly urge this Society to recognize the importance of this legitimate extension of its activities and responsibilities. Our expert knowledge and policies should be in advance and guide all such legislation.

I have the greatest confidence that the American Gynecological Society will continue as the wise and great leader in all the scientific, medical and social aspects of our specialty.

plication of fetal death during the period of observation. The last case was again a normal pregnancy, but this patient received large doses of estrogens on the sixteenth and fifteenth days before delivery and again during her first five post-partum days.

The patients were admitted from the ante-partum clinic and were hospitalized on the obstetric ward of the Bellevue Hospital during the period of study. Partial isolation was obtained by the use of an alcove on the ward. The diet was prepared in a small kitchen adjacent to the ward, used for no other purpose, and cooking and serving of the meals was in the hands of a nurse-dietitian whose sole duty was the care of these patients.

*The Intake.*—The patient was kept on a normal mixed diet, similar to that which she might have selected for herself at home. Three sets of meals differing somewhat from each other in actual make-up, but to a very slight extent in sodium and potassium content, were used. Diet "A" was made up of 228 gm. of carbohydrate, 75 gm. of protein, and 125 gm. of fat. The estimated content of potassium was 3.31 gm., of sodium 2.37 gm. Diet "B" contained 211 gm. of carbohydrate, 79 gm. of protein, and 125 gm. of fat. The estimated content of potassium was 3.32 gm., of sodium 2.36 gm. Finally a soft diet was planned for use on the day of labor and on the first post-partum day. The "labor diet" contained 168 gm. of carbohydrate, 80 gm. of protein, and 119 gm. of fat, the estimated potassium and sodium content being 3.33 gm. and 2.29 gm., respectively. The intake of sodium was intentionally placed at a rather low level so that no danger would be incurred by patients with edema. At the beginning of each three-day period food was purchased to make four complete diets of either the A or B type. This diet was fed for three days and a fourth complete day's feeding made up and cooked in an identical manner for analysis of sodium and potassium in the laboratory. To afford the patients some variety, a change was then made to the other diet, which was fed for another three-day period and a fourth set of three duplicate meals again made up for analysis. This alternation of these diets with an analysis every third day was continued throughout the tests. The figures for sodium and potassium on the intake side of the balance were thus based on actual analysis of duplicate food sample, and never upon estimated figures.

When labor began the patient was placed on a soft diet. If any food was refused during this period, the residue was preserved and analyzed and the amounts of sodium and potassium found were subtracted from the figures for the full day as obtained by analysis of a duplicate day's diet. In order to keep the intake as nearly constant as possible, known amounts of sodium and potassium chloride were administered in capsules to make up for the estimated deficiency due to food refused. These additions were of course accounted for in calculating the day's intake. The labors of all except one of the cases studied were fairly short and uncomplicated so that little difficulty was encountered in the feeding problem. Each patient had returned to one of the antepartum diets by the second post-partum day.

A liter of water was allowed daily in addition to that of fluid food material. The total daily fluid intake during the time of the A and B diets was 2,410 c.c.; during the two days of soft diet, 2,780 c.c.

Before making any measurements of either electrolytes or hormones, the patients were fed with one of the standard diets for several days, in most cases for a week. This served as a period of training of the patient in her routine and of stabilizing her intake and output. The graphs to be presented in each case begin only after this preliminary period had been completed.

#### COLLECTION OF EXCRETA AND OTHER SOURCES OF LOSS

The estimation of sodium and potassium loss from all possible sources during pregnancy, labor, and the puerperium is a complicated procedure and undoubtedly subject to several errors.

Urine was collected in especially cleaned containers, which were sodium and potassium free. These specimens during the ante-partum period were voided, but

years ago before this society De Snoo<sup>34</sup> presented figures to show that a low salt diet diminished the incidence of eclampsia, and more recently Strauss<sup>37-39</sup> has described the exacerbation of symptoms which follows the administration of sodium salts to toxemic patients with low plasma proteins.

2. Potassium has never been so clearly associated with pre-eclampsia. In high serum concentration this ion is known to have certain toxic effects<sup>31</sup> and may under special experimental conditions be responsible for elevations in blood pressure.<sup>5, 16, 23, 26</sup>

The principal reason for the inclusion of potassium in this study, however, was the contrast which it was hoped its behavior might afford to that of sodium, for the normal physiology of these two ions in the body is strikingly different. Potassium is the predominant basic ion within the cells, but is present in very small quantities in the blood plasma, whereas sodium is almost entirely restricted to the extracellular fluids. Furthermore certain endocrines, particularly the hormone of the adrenal cortex, produce opposite effects on these two ions, namely a retention of sodium and an excretion of potassium. A correlated study of the excretion of these two elements will help to distinguish between the intra- and extracellular sources of excreted water and may perhaps give some insight into adrenal function.

3. The placental hormones as isolated substances have for several years been a subject of research for a cause of toxemia. Various abnormalities such as an increase in prolactin concentration, a fall in estrogen<sup>32, 41</sup> and pregnandiol excretion and an alteration in the estrone:estriol ratios,<sup>33</sup> have been observed.

4. That a hormone was capable of causing a retention of sodium and of water was first conclusively demonstrated for a substance obtainable from the adrenal cortex,<sup>13, 14</sup> and now known as corticosterone. Between corticosterone and certain of the sex hormones there exists a close similarity of chemical structure. Suspecting that physiologic similarities might exist as well, Thorn and Engel<sup>42</sup> have injected estrone and estriol into dogs and have observed a cortinlike effect in the decreased excretion of sodium.

The sodium retaining effect of the estrogens and progesterones has already been given a clinical application in an explanation of the so-called menstrual edema (Thorn, Nelson and Thorn<sup>45</sup>). If the hormones of the menstrual cycle are capable of causing retention of sodium and of fluids, there is considerable reason at the outset to expect a more marked retention of these substances in pregnancy, when the hormones are effective in much greater concentration and over a much longer period of time.

A similar sodium retaining effect has been reported by Klodt<sup>18</sup> to follow the injection into rats of the gonadotropic hormone of the anterior lobe of the pituitary gland. Some delay in the onset of the decreased sodium excretion suggests the possibility that this effect might have been produced by the estrogens or progesterone released by the rat's own ovary as a result of stimulation by the injected anterior pituitary hormone. Until this is proved, however, the gonadotropic placental hormone must also be given consideration as a cause of sodium retention.

#### THE ORGANIZATION OF THE INVESTIGATION

In setting out to study this field, the period just before and after parturition seemed to us of most value. The separation of the placenta is followed by what must be the most abrupt endocrine changes that ever occur, so that the early puerperium is almost ideally adapted to the study of hormone-electrolyte relationships.

The sodium and potassium balances of six patients accordingly have been determined during the last few weeks ante partum, during labor, and the first ten post-partum days and correlated with the changes taking place in the concentrations of the various placental hormones during the same period. Three of these patients were untreated normal pregnant women. Two were toxemic patients, one developing the com-



requires a less intense final color than that used in the original method an extra dilution of the alkaline nitrite solution was made and the color was developed in the colorimeter test tube. Using this dilute solution, it was found necessary to allow one and one-half hours for full color development. The colors were read on a 520  $\mu$  filter. At this wave length they conformed to Beer's Law between 45 and 70 per cent absorption, and dilutions were always made to give colors falling within this range. Standard potassium solutions were run with each series of determinations. In analyzing urine and food the actual amount of potassium taken for precipitation was increased about ten fold over that used for plasma.

*Preparation of Materials.*—a. Plasma samples were prepared for analysis by precipitating the proteins with solid mercuric chloride and the phosphate with solid calcium hydroxide (Butler and Tuthill,<sup>4</sup> Holmes and Kirk<sup>15</sup>). For potassium analysis the method of Truszkowski and Zwemer<sup>46</sup> was used. Amniotic fluid was treated by the same procedure.

b. Food samples: The liquid and solid portions of a total daily diet, made up and cooked in a manner identical with the diet administered to the patient, were collected separately and weighed. Any meat in the diet was put through a meat chopper and added to the remainder of the solid food which was then put through the meat chopper twice more. The liquid food was next added to the ground solid food and the combined samples were vigorously shaken in a large jar to obtain a uniform suspension. A sample of about 100 gm. was immediately weighed into a Kjeldahl flask and then digested with sulfuric and perchloric acids. A small aliquot of this digest was evaporated to dryness in a crucible with care to keep the solution well below the boiling point. The residue was taken up in dilute nitric acid, and solid calcium hydroxide was added to remove the phosphate. Sodium was then determined on this solution.

Since it is necessary to remove the ammonium ion from the sample for potassium analysis, an aliquot of the alkaline calcium hydroxide solution was carefully evaporated to dryness. The residue was taken up in dilute nitric acid and potassium was determined on this solution. Tests showed that the solution at this point was free from both ammonium and chloride ions.

c. Urine samples were digested with sulfuric and perchloric acids in small crucibles with final evaporation to dryness. Further treatment was carried out as on the food samples.

d. Specimens of vomitus were analyzed as food, the entire amount being as a rule digested.

e. Feces were made up into a uniform paste with distilled water and were then sampled and digested by the methods outlined for the food.

f. The lochial specimens were brought to the laboratory on pads and were then disintegrated in distilled water. A measured amount of water was used and the mixture stirred until the pads were broken up, and the lochial material had dissolved. Sufficient fluid for analysis was drained off and treated according to the methods for blood plasma.

g. Breast milk was prepared for sodium analysis by treatment with solid calcium hydroxide and trichloroacetic acid to remove the phosphates and proteins, respectively. For potassium analysis the proteins and chlorides were precipitated in the manner noted for the plasma determinations.

#### THE ACCURACY OF SODIUM AND POTASSIUM DETERMINATIONS

The errors in the actual chemical procedures on food and excreta are relatively small, for it was found that duplicate analyses agreed to within  $\pm 1$  per cent and  $\pm 2$  per cent of the mean for sodium and potassium, respectively. Greater errors, however, were certainly involved in the collection and preparation of material for analysis.

1. The error in plasma determinations on amounts as small as those used is also larger. A special difficulty is encountered in the measurement of plasma potassium, where as a result of the passage of potassium into the plasma from hemolyzed cells the determination is subject to a possible positive error of perhaps 10 per cent.

2. Lochial figures are unquestionably less accurate than those for food and urine because of the method of collection and extraction from the pads. However,

immediately after labor a retention catheter was inserted and the urine collected by this means during the first week of the puerperium so that contamination with the lochia could be avoided.

Feces were obtained by spontaneous evacuation or following the use of distilled water enemas.

Vomiting occurred in two cases during labor. The sodium and potassium figures on the vomitus were determined and subtracted from the day's intake.

*Milk.*—Only two patients were allowed to nurse their babies. In each instance the babies were weighed before and after nursing, and samples for analysis were obtained by pumping the breast at each feeding. The total daily loss was of course the amount found in the sample added to the estimated amounts obtained by the baby.

The lochia afforded special difficulties. Vulval pads made of disintegrating material were packed in a large glass jar which was sterilized and weighed. After use the pads were returned to the jar which was again weighed, the increase being regarded as the weight of the lochia.

*Amniotic Fluid.*—When the cervix had attained about three fingers' dilatation during labor the patient was placed on a bed pan and the membranes ruptured. A sufficient quantity of relatively uncontaminated amniotic fluid was then obtained for analysis. The total volume of amniotic fluid was taken as the amount lost at this time, plus the increase in weight of vulval pads worn thereafter until delivery, plus the fluid lost immediately after delivery. The sodium and potassium of the amniotic fluid was not, however, added to the balance figures, because this was regarded as already outside of the maternal system at the time of its loss, and there was little reason to suppose its volume had greatly changed during the antepartum period of study.

Blood lost after the delivery of the baby was collected, analyzed and applied to the negative side of the balance. It accounted for a slight increase in sodium loss notable in one or two cases on the day of labor. The blood taken for specimens during the course of the study was also considered in the balance, since with the large specimens needed for hormone analysis the electrolyte loss by this means is not negligible.

Loss by perspiration has not been taken into consideration. Since we were interested particularly in contrasting trends of electrolyte excretion before and after labor and the factor of perspiration was presumably more or less constant, the omission of the study of sodium and potassium loss by this channel did not seem to introduce any serious error. Freyberg and Grant<sup>9</sup> have reported a daily loss by perspiration of 0.133 to 0.179 gm. of potassium and 0.071 to 0.209 gm. of sodium. A daily loss of 0.15 gm. of potassium and 0.10 gm. of sodium may perhaps be assumed.

#### TECHNICAL DETAILS OF CHEMICAL DETERMINATIONS

The work required determinations of sodium and potassium on a variety of materials and the assay of estrogens, gonadotropic hormones and pregnandiol.

*Determinations of Sodium and Potassium.*—a. Sodium was determined by precipitating it as sodium zinc uranyl acetate according to the method of Ball and Sadusk.<sup>2</sup> The precipitations were allowed to stand over night, after which they were vigorously stirred in a water bath maintained at 14° to 16° C. The amount of precipitate was estimated by the colorimetric method of Salit.<sup>29</sup> The colors obtained by this procedure, after allowing forty-five minutes for color development, were read on an Evelyn photoelectric colorimeter using a 520  $\mu$  filter. Under these conditions the light absorption conformed to Beer's Law over a concentration range corresponding to 25 to 80 per cent absorption. This was not found to be true using other filters. Standard sodium solutions were run with each series of determinations.

b. Potassium was determined by the method of Truszkowski and Zwemer.<sup>46</sup> The final colors were read on the Evelyn photoelectric colorimeter. Since this instrument

is plotted in relation to the days before and after delivery. The values for pregnandiols are also plotted directly on the ordinates as milligrams.

The estrogens and the prolan figures are plotted in rat units on a logarithmic scale which emphasizes the differences in the lower values and minimizes those between the higher ones. This was a necessary method in order to make charts of a practical size and shape, but it was also consistent with the ratios of the dose levels used in the assay of the unknown extract.

Furthermore it is not improbable that from a physiologic standpoint the difference between 50 and 100 units is more comparable with the difference between 1,000 and 2,000 than between 1,000 and 1,050.

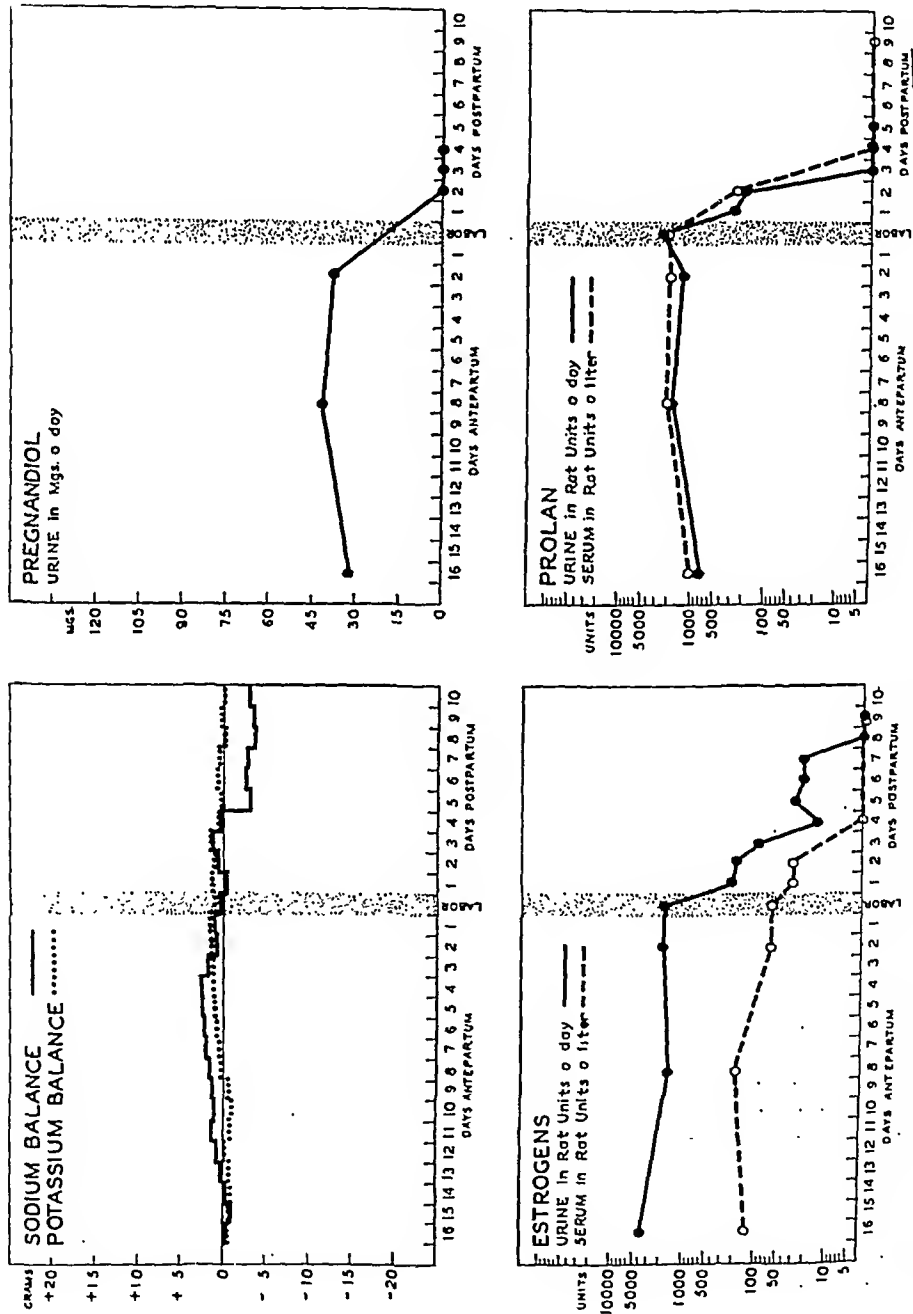


Chart 1.—Correlation of sodium and potassium balances with hormone levels in a normal pregnancy and puer-

the amounts of sodium and potassium contributed to the balance by the lochia are so small as to make any error incurred in the balance almost negligible.

3. The determinations on food are subject to two errors in addition to those inherent in the technical method. There is one error involved in the weighing, preparing and cooking the supposedly identical diets and a second in the sampling for analysis. The latter error was reduced by using large samples (100 gm.) of the mixed food. The former can be kept down only by painstaking attention to detail by the person in charge of the preparing of the food.

To test the accuracy of the figures arrived at for the food, the dietitian was instructed to make independently and send separately to the laboratory for analysis four complete twenty-four-hour feedings. Two samples of each of these were taken for analysis and each sample run in duplicate. The percentage deviation from the mean of the two samples was 1.2 per cent for sodium and 3.9 per cent for potassium. The percentage deviation of the mean from the average for the four separate diets, in general a measure of all errors involved, was 3.7 per cent for sodium and 4.8 per cent for potassium.

#### TECHNIQUE OF HORMONE DETERMINATION

Hormone assays were carried out with few changes from the technique described in a previous paper (Taylor and Scadron<sup>41</sup>). A few alterations in method alone need be noted.

1. Estrogens: Owing to the small quantities of estrogens present in post-partum specimens of urine, these had to be extracted after hydrolysis to obtain sufficiently concentrated material for assay. In order to make the ante-partum specimens comparable these also were extracted. The technique used was that of Kurzrok and Ratner<sup>22</sup> in which ethyl acetate is used as a solvent.

For assay of the urinary estrogen, the number of rats used for each level was increased to eight except for specimens from the latter post-partum days when the estrogen content of the urine is too low to permit the use of so many. One rat unit was said to be present when the vaginal spreads of 6 of the 8 animals showed complete cornification. In our experience one such rat unit is equivalent to about 3.5  $\gamma$  of estrone.

For the serum four rats were injected with the estrogen content of 4 c.c. of blood serum divided into four doses. A full rat unit of the type described is rarely present in 4 c.c. of serum so that degrees of estrus dependent on the character of the cell mixture of the vaginal spread were noted on a scale of 0 to 4 as described by Frank.<sup>8</sup> On the basis of experience obtained from the injection of 800 rats equivalents have been worked out so that partial reactions might with some justification be expressed as given fractions of a rat unit. The method is crude and certainly yields only approximate values. The blood estrogen figures obtained from specimens before and after labor are, however, comparable at least on a qualitative basis. The low values for serum estrogen noted may be explained partly by this method of calculation, partly by the fact that sera were not hydrolyzed so that only the free hormone was being measured.

2. Prolan determinations on ante-partum specimens were made exactly as in the previous report. All sera were extracted to remove contaminating estrogens. Post-partum specimens of urine after the second post-partum day, owing to the large volumes which had to be used to demonstrate one unit, were precipitated with 10 per cent tannic acid according to the method of Levin and Tyndale<sup>24</sup> instead of with alcohol.

3. Pregnanediol in the urine was determined by the method of Venning.<sup>47, 48</sup> Two acetone precipitations were routinely performed, but melting point determinations were begun only after the first four cases had been completed.

#### THE CONSTRUCTION OF THE CHARTS

The relationship of the hormones to the balance of sodium and potassium is shown in Charts 1 to 6. In the sodium and potassium chart the net daily gain or loss of these elements, with all measured sources of intake and excretion considered,

CASE 2.—M. G. (History No. 85113), admitted on Sept. 5, 1938. This was a 36-year-old para ii, who had had her last menstrual period on Nov. 12, 1937, and a subsequently normal pregnancy as observed in the ante-partum clinic. Her course in the hospital was also normal, and on September 27 after a labor of eleven and one-half hours she was delivered of an 8 pound, 11 ounce male child. The blood loss at delivery was 200 c.c. The patient attempted to nurse her baby, but her supply of milk was scant. Her post-partum course was entirely normal.

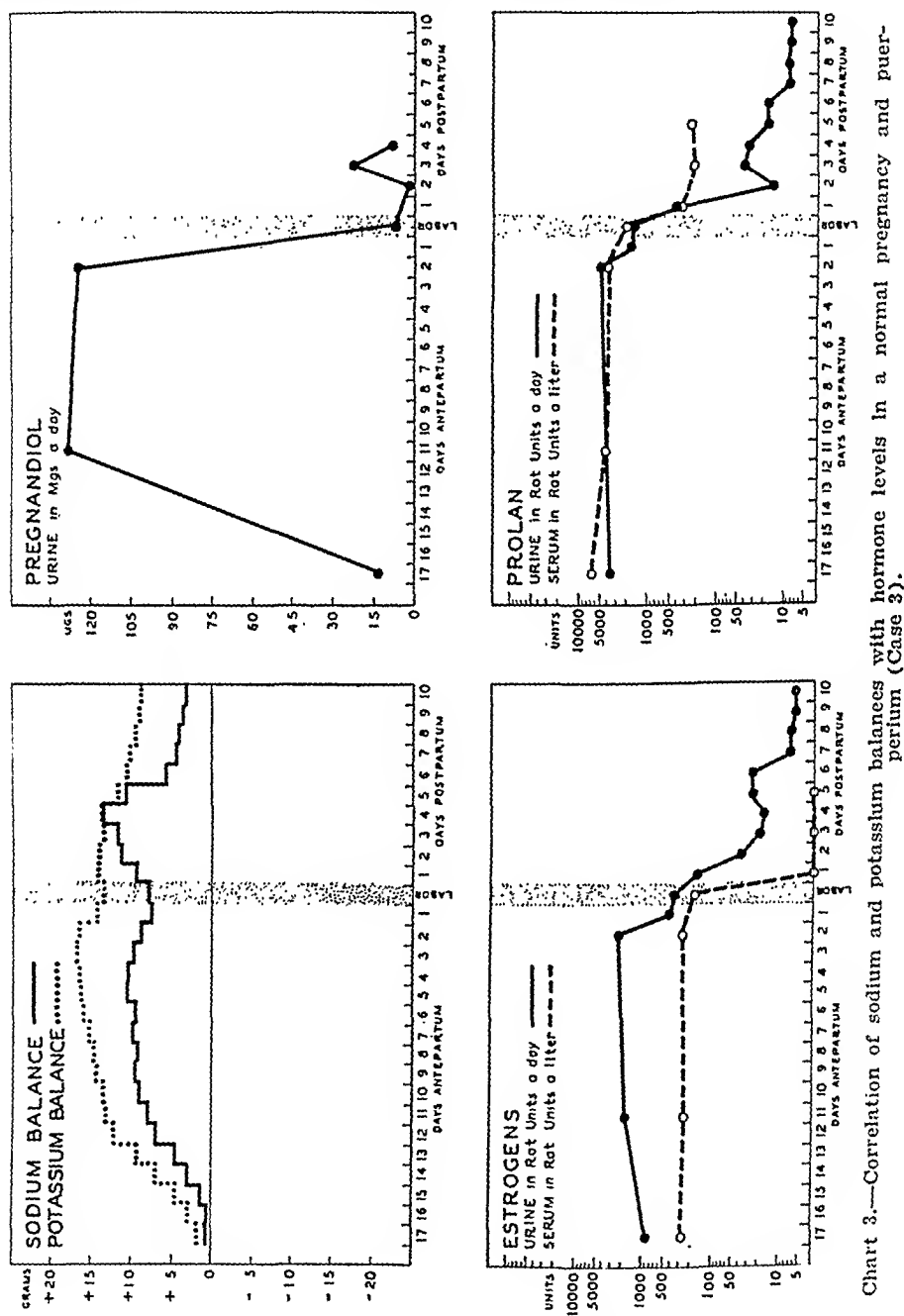
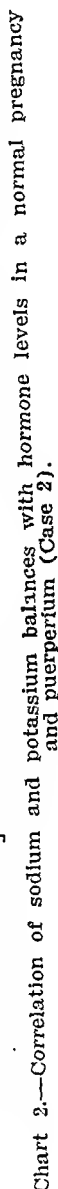


Chart 3.—Correlation of sodium and potassium balances with hormone levels in a normal pregnancy and puerperium (Case 3).

CASE 3.—M. P. (History No. 122209), admitted Oct. 11, 1938. This patient was a 17-year-old primigravida who gave a history of a last menstrual period on Jan. 25, 1938 and a normal pregnancy thereafter. This patient had been living under restricted economic conditions before admission, and there was considerable question

Three women admitted toward the end of a normal gestation were studied during the last weeks of their pregnancy, during labor, and during their first ten post-partum days.



CASE 1.—M. M. (History No. 108879), admitted on April 10, 1938. This patient, a 17-year-old primigravida, had been followed throughout a quite normal pregnancy in the ante-partum clinic. Her last menstrual period was on July 17, 1937. She was normally delivered on May 5, 1938 of a 7 pound, 14 ounce male after a labor of sixteen hours. The blood loss at delivery was 513 c.c. She did not nurse her baby. The post-partum course was complicated by low grade fever, proteinuria and pyuria as a result of cystitis perhaps due to the retention catheter.

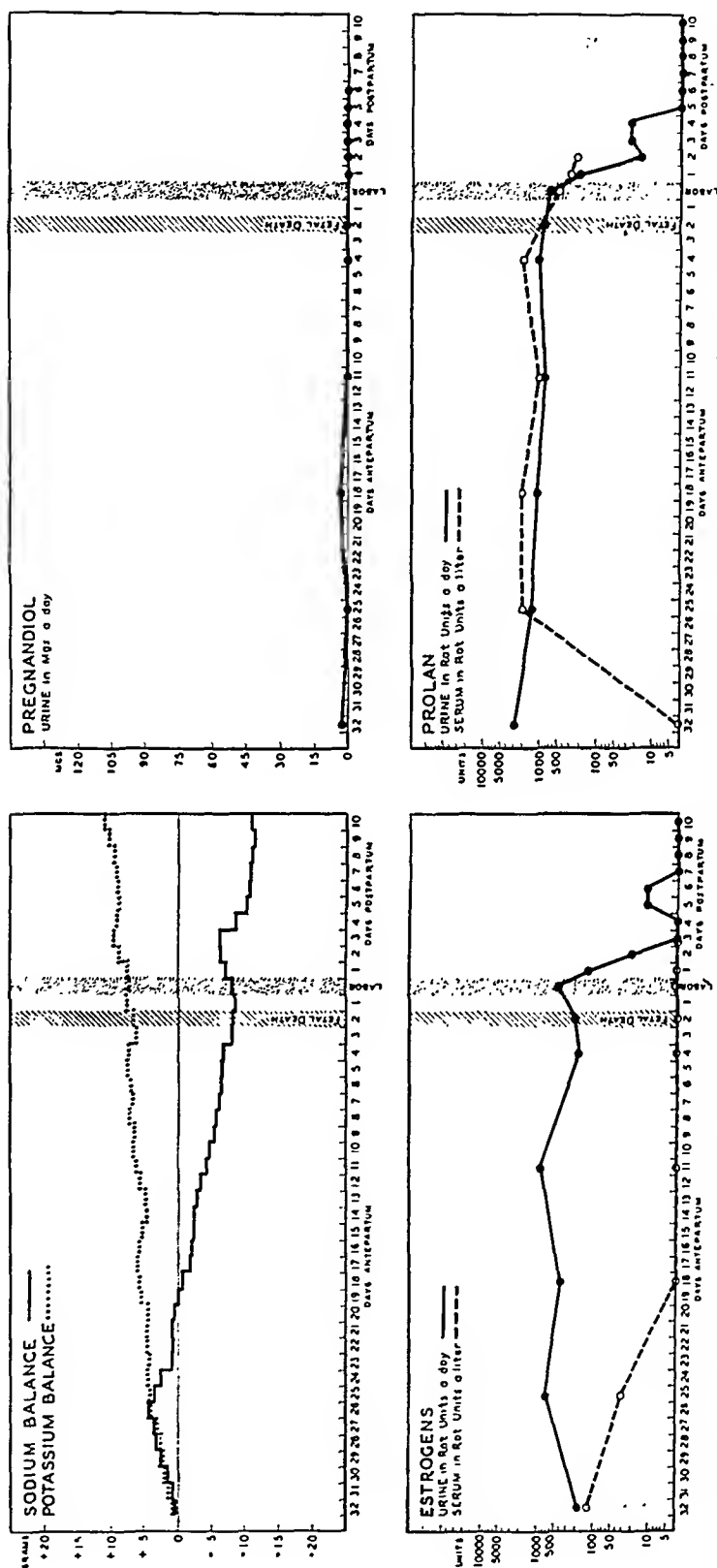


Chart 5.—Correlation of sodium and potassium balances with hormone levels in a patient with pre-eclampsia and fetal death (Case 5).

of the adequacy of her customary diet. Her ante-partum course in the hospital was normal, but her labor which was prolonged to fifty hours, on account of slight disproportion, was terminated by midforceps. The blood loss amounted to 375 c.c. The baby, an 8 pound 10 ounce female, was nursed. The post-partum course was nonmorbidity and otherwise normal.

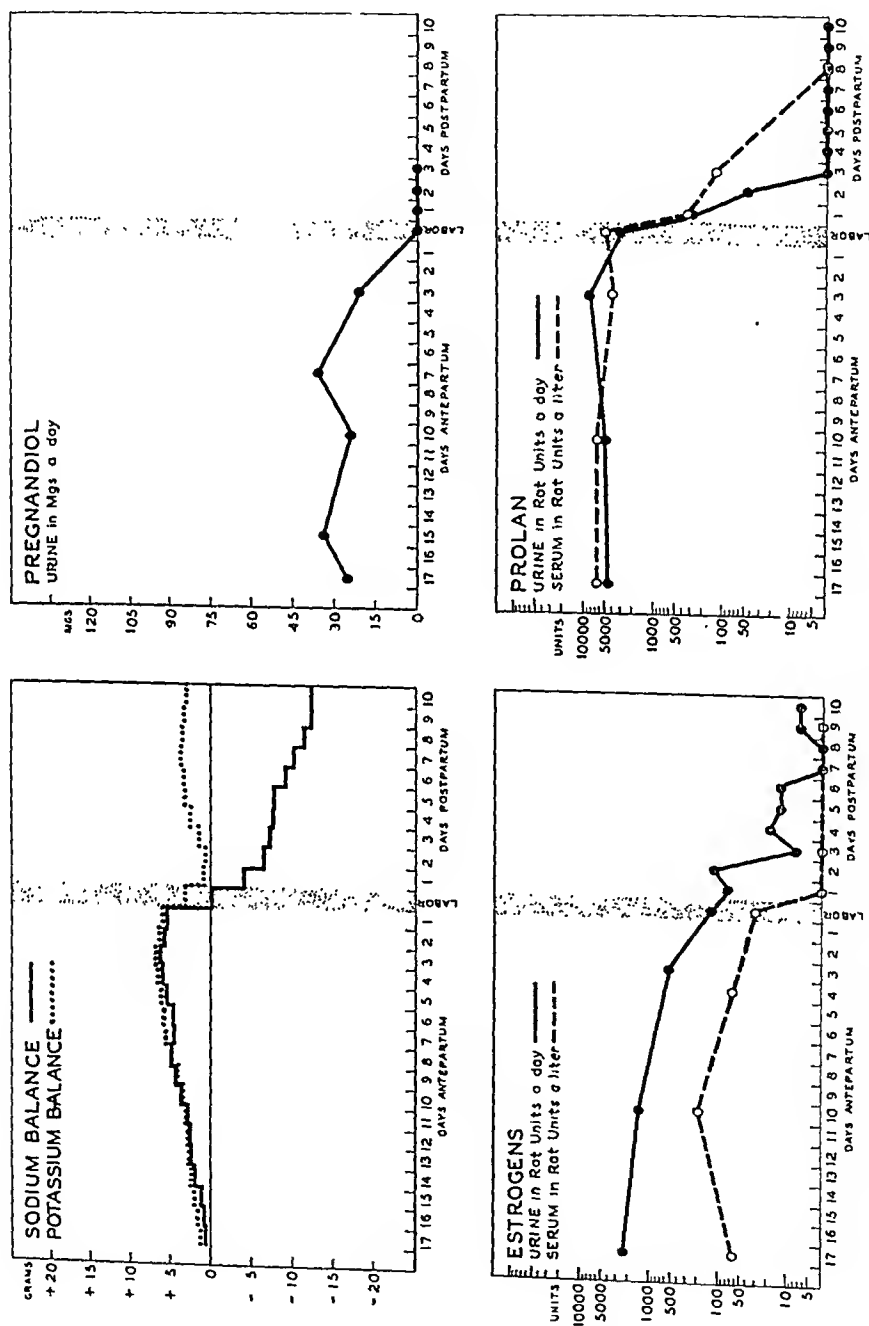


Chart 4.—Correlation of sodium and potassium balances with hormone levels in a patient with pre-eclampsia (Case 4).

Certain features were common to the three normal cases (Charts 1 to 3). The estrogens before labor gave values in the urine varying from 200 to 3000 rat units per liter or in a range similar to those previously reported (Taylor and Scadron<sup>41</sup>). The values dropped very abruptly after labor and by the third day the amounts obtained were reduced practically to those of nonpregnant women.



Pregnandiol values in the ante-partum period also varied in a wide range from 13 to 120 mg. in a twenty-four-hour urine specimen. The highest values were possibly errors, since melting point determinations were not made on these particular specimens. Pregnanediol disappeared even more quickly than the estrogens and was as a rule absent by the third post-partum day.

Prolan values before delivery ranged from 750 to 4,700 rat units a day in the urine and from 2,000 to 6,667 rat units per day in the serum. This substance also fell rapidly after labor, but 25 units could often be found until the third or fourth day and the effects of traces were evident in the ovaries of the test animals injected even with extracts of eighth- or ninth-day urines.

The sodium balance was slightly, but almost consistently, positive in all three cases up until the time of labor. This is in agreement with previous studies.<sup>6, 10, 17</sup> The trend was somewhat irregular during the first few post-partum days with at first perhaps a little retention. On the fifth or sixth day, however, there was in each case a pronounced negative balance due chiefly as can be seen from Table I, II and III to an increased excretion of sodium in the urine. In two cases the gains in the ante-partum period were relatively slight, but in one the total amounted to 13.5 gm. in twenty days. This was the patient who, it was believed, had been living on a generally deficient diet before she was admitted to the hospital. The potassium tended to be retained in a little larger amounts before labor and to be lost more slowly afterwards than the sodium.

*Comment.*—In the ante-partum period no correlation was possible between the actual amounts of hormone present in the urine or blood and the rate of sodium and potassium retention.

The striking feature common to all cases was the post-partum increase in sodium loss, chiefly in the form of sodium excretion in the urine, which usually began on the fifth post-partum day or shortly after the estrogens and progesterone had fallen to levels for nonpregnant women (Tables I to III). A slight retention during the first two or three post-partum days was also perhaps a significant finding.

#### RELATION OF SODIUM AND POTASSIUM BALANCE TO HORMONE CONCENTRATION IN A CASE OF PRE-ECLAMPTIC TOXEMIA

One case of relatively severe pre-eclamptic toxemia ending in the delivery of a normal child was studied in a similar manner.

CASE 4.—L. D. (History No. 112475), admitted on June 4, 1938. This patient was a twenty-year-old primigravida, giving Sept. 1, 1937 as the date of her last menstrual period. She had been followed in the ante-partum clinic from her second month. Her course had been quite normal until near the end of her eighth month, when she suddenly developed hypertension, moderate edema of the lower extremities, and proteinuria. During her month's stay in the hospital before labor her condition remained essentially unchanged, large quantities of protein being constantly present in the urine and the blood pressure varying from 190/120 to 138/100 (see Table IV). On July 6, 1938 after ten hours of labor she was spontaneously delivered of a 5 pound, 6 ounce female child with a blood loss of 175 c.c. She did not nurse the baby. Her post-partum course was uncomplicated. The signs of hypertension and proteinuria tended to lessen and on her discharge on the tenth day the blood pressure was 136/90, and the urine contained only 1.2 gm. of protein.

The hormone curves for this patient (Chart 4) were in general similar to those for the normal cases. Relatively low estrogens and pregnandiol and high prolactin concentrations were present, a finding said to be a characteristic of the disease from which the patient was suffering.

Sodium was retained before delivery in this case as in the normal patients. The post-partum curve corresponded in form to that of the normal cases, but showed a greater loss of sodium. The great excretion of salt in the post-partum period

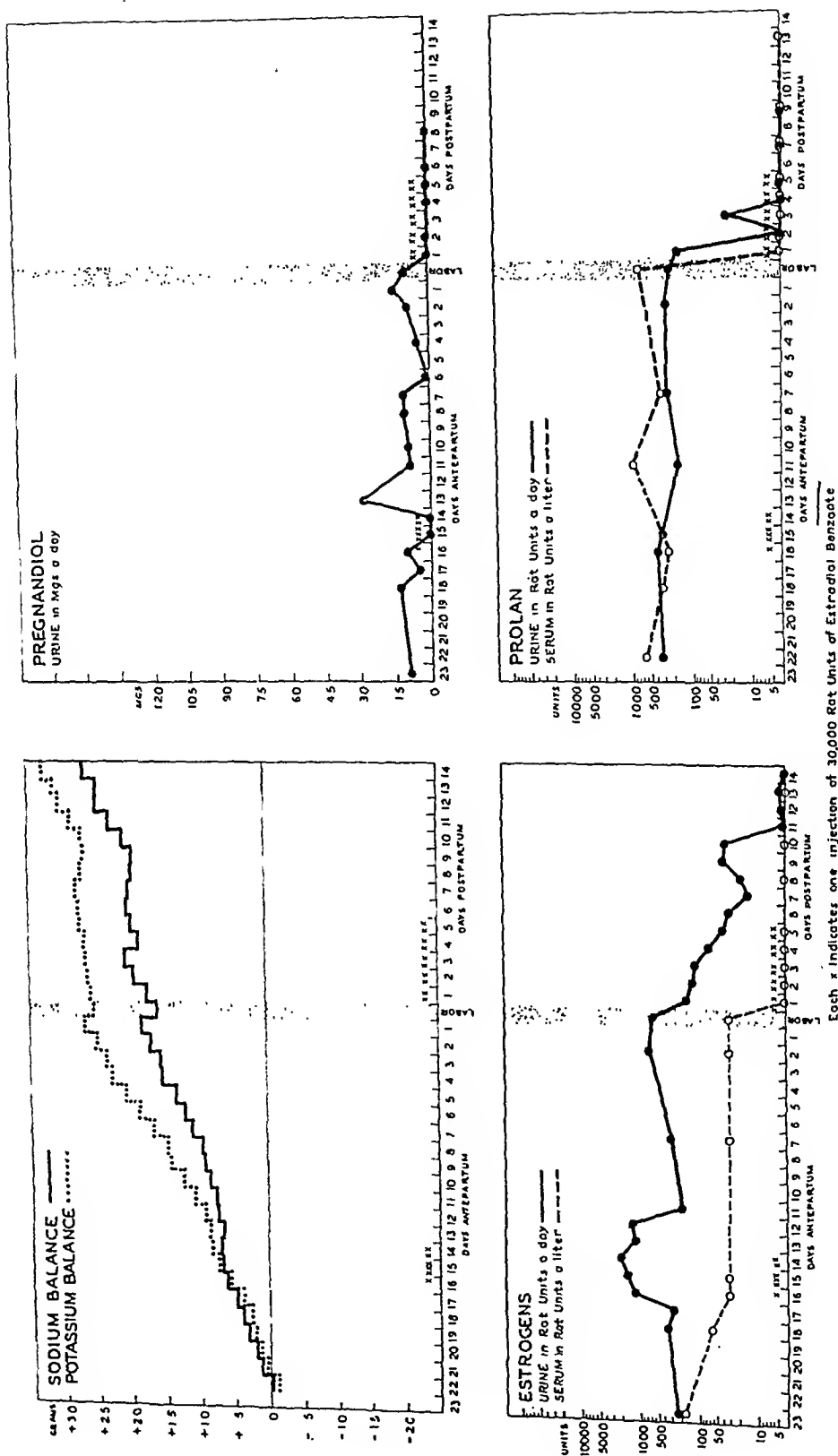


Chart 6.—Correlation of sodium and potassium balances with hormone levels in a normal patient receiving estradiol benzoate (Case 6).

TABLE II. CLINICAL DATA WITH SODIUM AND POTASSIUM VALUES IN PATIENT M. G. (CASE 2)

CLINICAL				SODIUM					POTASSIUM					
DAYS	BLOOD PRES-SURE	WEIGHT IN POUNDS	PROTEIN-URIA GM./LITER	URINE VOLUME C.C./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY	MILK GM./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	MILK GM./DAY	LOCHIA GM./DAY
13		147½	0	490	310	1.47	0.057			22.4	1.48	0.061		
12		147½	0	620		1.66	0.057				2.35	0.061		
11		147	0	640		1.70	0.057				1.73	0.061		
10		147½	0	2360		2.38	0.063				3.46	0.506		
9	108/80	147½	0	1740		1.98	0.063				2.46	0.506		
8		148½	0	1320		1.92	0.063				2.78	0.506		
7		148½	0				0.063				5.20	0.506		
6		149½	0	2760	321	3.54	0.063			25.6		0.506		
5		148½	0	1200		1.67	0.027				2.64	0.144		
4		149	0	1280		1.96	0.027				2.75	0.144		
3		148½	0	1340		1.63	0.027				2.64	0.144		
2		148½	0	1460		1.82	0.027				2.69	0.144		
1	114/82	149½	0	1480		1.78	0.027				2.01	0.144		
Labor A		149½	0	900	322	1.03		0.40*		21.6	1.91		0.30*	
Labor B				195	327	0.25	0.010	0.104		20.1	0.82	0.033	0.051	
1	108/74		Trace	2880	321	3.68	0.010	0.090		17.5	4.01	0.033	0.090	
2			0	2900	321	3.44	0.010	0.092	0.034	19.0	3.75	0.033	0.094	
3	106/70		0	2030	327	1.83	0.010	0.092	0.044	16.8	3.02	0.033	0.094	0.015
4			0	2510	329	2.62	0.010	0.092	0.035	15.9	3.08	0.033	0.094	0.019
5			Trace	1830	320	2.91	0.049	0.068	0.038	16.7	2.87	0.033	0.103	0.029
6	114/78		Trace	3020	316	4.46	0.049	0.068	0.210	17.5	4.20	0.033	0.103	0.152
7			Trace	2200	287	2.23	0.049	0.068	0.148	16.0	2.89	0.033	0.103	0.207
8		128	Trace	1940	311	2.51	0.049	0.072	0.114	20.4	3.72	0.033	0.403	0.236
9		127	Trace	1330	310	1.91	0.049	0.072	0.139	18.3	2.63	0.033	0.403	0.360
10		128		1050	316	1.27	0.049	0.072	0.174	16.8	1.72	0.033	0.403	0.394

\*Blood loss at delivery.

Labor A, Until delivery.

Labor B, Remainder of twenty-four hours after delivery.

TABLE I. CLINICAL DATA WITH SODIUM AND POTASSIUM VALUES IN PATIENT M. M. (CASE 1)

CLINICAL										SODIUM				POTASSIUM			
DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEIN-URIA GM./LITER	URINE VOLUME C.C./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY					
16	94/64	131½	Trace	2300	298	2.72	0.001		19.0	3.54	0.146						
15	120/60	131½	Trace	2210		3.42	0.001			3.15	0.146						
14		131½	Trace	2170		2.00	0.001			3.31	0.233						
13	108/54	131½	Trace	2060		2.25	0.0006			2.87	0.233						
12	92/62	132½	Trace	1500		1.68	0.0006			3.90	0.233						
11	112/64	132½	Trace	1680		1.95	0.0006			3.44	0.276						
10	120/64	132½	Trace	2340		2.69	0.063			2.72	0.276						
9		132½	Trace	2150		2.10	0.063			2.78	0.276						
8		132	Trace	1990		1.99	0.063			2.70	0.276						
7		132½	Trace	1910		2.23	0.063			2.88	0.276						
6		132½	Trace	1860		2.49	0.063			3.23	0.276						
5		132½	Trace	2020		2.48	0.063			2.79	0.276						
4		132½	Trace	2290		2.10	0.063			2.63	0.276						
3		133½	0	2250	300	2.73	0.063		18.7	2.83	0.276						
2		131	Trace	2440		2.99	0.063			2.70	0.585	0.790*					
1	112/84	132½	Trace	1940		1.77	0.19	0.945*									
Labor																	
	112/66	132½	0	2340	301	1.91	0.19	0.606	16.6	3.17	0.585	0.058					
1	106/70		Trace	1150	305	0.861	0.008	0.248	17.4	2.40	0.165	0.124					
2	110/74		Trace	1970	312	0.985	0.008	0.267	17.5	3.29	0.165	0.165					
3	102/64		+	1870	310	1.34	0.008	0.060	18.8	2.79	0.165	0.287					
4			+	2700	315	3.33	0.008	0.060	17.1	3.87	0.165	0.287					
5		120½	++	3470	309	5.46	0.008	0.060	17.5	3.37	0.165	0.287					
6	118/74	116½	+	2230	308	1.85	0.008	0.092	18.0	2.90	0.165	0.113					
7		115½	+	2410	326	2.24	0.010	0.092	16.3	3.43	0.318	0.113					
8		115½	++	2120	330	2.67	0.010	0.092	17.7	3.48	0.318	0.113					
9		115½	++	1900	325	1.92	0.009	0.092	18.1	2.71	0.378	0.113					
10		116	+	2020		1.74	0.009	0.092		3.26	0.378	0.113					

\*Blood loss at delivery.

TABLE IV. CLINICAL DATA WITH SODIUM AND POTASSIUM VALUES IN PATIENT L. D. TOXEMIA (CASE 4)

DAYS	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEIN-URIA GM./LITER	URINE VOLUME C.C./DAY	SODIUM			POTASSIUM		
					PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY	PLASMA MG. %	URINE GM./DAY
17	162/116	125½	3.8	1190	337	1.39	0.009		20.9	2.27
16	150/114	125½	4.0	1780		1.89	0.009			2.85
15	170/120	126½	3.2	1830		2.00	0.013			2.91
14	160/118	125½	3.6	1310		1.43	0.013			2.57
13	164/110	126½	3.6	1720		1.89	0.013			2.92
12	156/114	126½	3.6	1560		2.27	0.013			3.06
11	150/102	125½	4.3	1830		1.98	0.013			2.89
10	190/120	125½	5.4	1300	339	1.65			23.6	2.81
9	175/115	125	6.0	1410		1.82				2.97
8		126	5.4	1540		1.90				2.56
7		127½	4.0	2080		2.52	0.010			2.50
6	158/124	126½	4.2	1580		2.40	0.010			2.99
5	140/110	126½	4.6	1530		2.44	0.010			3.07
4	140/110	127½	4.6	1510		2.32	0.010			2.89
3	146/104	126½	4.2	2120	345	2.65	0.010		22.4	3.20
2	140/104	125½	4.2	1810		2.59	0.010			2.86
1	140/102	125½	4.4	1510		2.51	0.010			2.89
Labor A.	188/118		6.9	160	321	3.95	0.010	0.310*	22.4	0.41
Labor B.	176/118		2.9	1950	318	3.02	0.012	0.284	21.1	2.89
1	196/128		1.9	3130	319	5.61	0.012	0.223	22.6	3.38
2	148/100		1.5	2330	299	4.47	0.012	0.150	18.3	2.47
3	148/90		2.4	1820	339	2.91	0.012	0.150	28.4	2.41
4	140/90		2.9	1700	349	2.64	0.012	0.150	21.5	2.37
5	146/98		1.9	2040	334	2.35	0.012	0.078	24.3	2.34
6	122/94	108½	1.7	3020	325	3.42	0.012	0.078	25.0	2.90
7	136/102		1.7	2030	326	2.66	0.011	0.078	23.9	2.96
8	140/80	104½	1.8	1940	324	3.16	0.011	0.101	22.1	3.20
9	126/84	104½	1.2	1520	290	2.64	0.011	0.101	24.5	3.12
10	136/90	105½	1.2	1190		1.89	0.011	0.101		3.48

\*Blood loss at delivery.

Labor A, Until delivery. Labor B, Remainder of twenty-four hours after delivery.

TABLE III. CLINICAL DATA WITH SODIUM AND POTASSIUM VALUES IN PATIENT M. P. (CASE 3)

TABLE III. CLINICAL DATA WITH 800														
CLINICAL					SODIUM				POTASSIUM					
DAYS	BLOOD PRES-SURE	WEIGHT IN POUNDS	PROTEIN-URIA GM./LITER	URINE VOLUME C.C./DAY	PLASMA MG. %	URINE GM./DAY	FECEs GM./DAY	LOCHIA GM./DAY	MILK GM./DAY	PLASMA MG. %	URINE GM./DAY	FECEs GM./DAY	LOCHIA GM./DAY	MILK GM./DAY
17		122½	0	860	311	1.28	0.06			25.6	1.00	0.06		
16	114/86	122½	0	1250		2.20	0.08				1.76	0.11		
15		122	0	1545		1.33	0.08				1.33	0.11		
14	118/80	123½	0	1315		1.17	0.08				0.73	0.11		
13		122½	0	985		0.87	0.08				0.56	0.11		
12		122½	0	965		0.46	0.08				0.51	0.11		
11	112/80	122½	0	1065		1.43	0.08				1.57	0.11		
10		123½	0	1775	333	1.22	0.08			23.0	2.54	0.11		
9	112/82	123½	0	1755		1.88	0.08				2.01	0.05		
8		123½	0	1935		2.84	0.02				2.67	0.05		
7		123½	0	1610		1.69	0.02				2.36	0.05		
6		123½	0	2045		2.99	0.02				2.60	0.05		
5		123½	0	1825		1.87	0.02				2.21	0.05		
4	112/82	123½	0	1970		2.88	0.02				2.66	0.05		
3			0	1840		3.28	0.02			23.4	2.63	0.05		
2 A	114/90		0	1985	368	2.39	0.02				2.75	0.05		
2 B			0	390		0.98	0.02				0.46	0.02		
1			0	1750	349	1.57	0.01			24.7	2.30	0.02		
Labor A	136/84		0	205		0.13		0.91*			0.58		0.65*	
Labor B			Trace	1415	337	0.35	0.01	0.19		24.6	2.23	0.02	0.05	
1			0	1580	343	0.21	0.01	0.09	0.01	24.2	2.57	0.02	0.02	
2	118/70		0	1390	345	0.15	0.01	0.09		21.8	2.56	0.02	0.02	0.003
3			0	1945	348	1.84	0.01	0.07	0.01	23.2	2.86	0.02	0.07	0.04
4	128/90		0	1680	343	1.26	0.19	0.07	0.03	21.3	1.60	0.51	0.07	0.17
5			0	2490	357	5.08	0.19	0.07	0.05	21.2	3.60	0.51	0.07	0.32
6			0	2460	345	7.10	0.02	0.05	0.01	21.3	3.03	0.13	0.04	0.29
7			Trace	1395	334	3.71	0.02	0.05	0.02	21.0	2.65	0.13	0.04	0.38
8			0	1515	334	2.89	0.02	0.05	0.06	18.5	2.80	0.13	0.04	0.34
9		111	0	1715	338	3.09	0.02	0.05	0.02	19.3	2.73	0.13	0.04	0.31
10		109	0	1640	332	2.73	0.02	0.05	0.01	21.6	2.34	0.13	0.04	0.32

\*Blood loss at delivery.

2A, Before onset of labor; 2B, after onset of labor.

Labor A, Until delivery. Labor B, Remainder of 24 hours after delivery.

TABLE V. CLINICAL DATA WITH SODIUM AND POTASSIUM VALUES IN PATIENT M. A. TOXEMIA (CASE 5)

DAYS	BLOOD PRESSURE	CLINICAL			SODIUM				POTASSIUM			
		WEIGHT IN POUNDS	PROTEIN-URIA GM./LITER	URINE VOLUME C.C./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY
32	140/110	127½	+++	1450	334	2.87	0.01		18.9	2.56	0.02	
31	186/114	127	+++	1585		2.70	0.01			2.44	0.02	
30	146/104	127½	+++	990		2.42	0.01			2.51	0.02	
29	182/114	127½	1.4	1675		2.37	0.01			3.01	0.02	
28	174/112	129	2.6	1560		2.58	0.01			2.62	0.02	
27	172/112	129½	2.2	1795		2.83	0.01			2.68	0.02	
26		129½	2.4	1660		2.61	0.01			2.27	0.02	
25		130	2.6	1440	333	2.93	0.01		25.4	2.73	0.02	
24	158/108	130½	2.8	1450		3.21	0.01			2.75	0.02	
23	146/102	130	2.6	1410		3.84	0.01			3.31	0.02	
22	162/108	130½	2.2	1850		2.94	0.01			2.65	0.02	
21		130					0.01				0.02	
20	138/ 90	129½	2.0	1735		3.40	0.01			3.00	0.12	
19	164/106	129	2.2	1325		2.58	0.01			2.80	0.12	
18	162/106	129	2.0	1575	303	2.83	0.01		29.3	3.21	0.12	
17	182/114	129½	3.6	1645		3.48	0.01			2.95	0.12	
16	150/102	128½	3.0	1595		2.41	0.02			2.66	0.33	
15	160/112	129	2.4	1730		2.49	0.02			2.98	0.33	
14	166/116	129½	2.0	1760		2.31	0.02			2.90	0.33	
13	160/116	129½	2.8	1700		2.90	0.02			2.76	0.33	
12		129	3.0	1660		2.81	0.01			2.42	0.14	
11	164/116	129½	2.4	1830	328	3.26	0.01		25.2	2.48	0.14	
10	158/120	129	2.6	1565		2.83	0.01			2.79	0.14	

in previously edematous patients is a well-recognized phenomenon (Schwarz and Dieckmann<sup>30</sup>). The potassium again showed a positive ante-partum balance and a less marked tendency to fall after delivery. The potassium curve in fact diverged quite markedly from that for sodium in the post-partum period.

*Comment.*—The greater sodium loss in the puerperium of this as well as in other pre-eclamptic patients is no doubt due to the disposal of extracellular edema fluid. There was of course no evidence of excessively high ante-partum estrogens or pregnandiol to give an explanation for the greater sodium retention in this patient with toxemia. The period of greatest post-partum sodium loss, however, again closely followed the disappearance of the hormones from the circulation.

RELATION OF SODIUM AND POTASSIUM BALANCE TO CHANGING HORMONE CONCENTRATION IN A TOXEMIC PATIENT WITH INTRAUTERINE FETAL DEATH

A fetal death occurring in the course of the study of a second patient with pre-eclampsia afforded an unexpected opportunity to study the effects produced by diminution in hormone concentrations on the behavior of electrolytes without the complicating factors incidental to delivery (Chart 5).

CASE 5.—M. A. (History No. 125221), admitted Nov. 10, 1938. This patient, a twenty-five-year-old primigravida, gave a history of a last menstrual period on April 15, 1938, and a normal pregnancy observed in the ante-partum clinic until the seventh month. At that time she developed headache and nausea and vomiting with hypertension, proteinuria, and edema. During the hospital stay which followed she improved symptomatically, but the blood pressure level and urinary findings remained unchanged (Table V). The fetal heart was last heard on Dec. 21, 1938, three days before the onset of labor. On December 24 she was delivered of a three-pound macerated stillbirth after a labor of four hours. There was essentially no blood loss and the amniotic fluid had been reduced to a few ounces of thick meconium-like material. The hypertension began to improve on the sixth day, and on the eighteenth post-partum day, the blood pressure reading was 114/78 and the protein in a twenty-four-hour urine was reduced to 1 gm. At her last visit to the follow-up clinic two months after her delivery, the urine was normal and the blood pressure was 120/74.

The hormone assays in this patient revealed changes which may be characteristic of impending or actual fetal death. The estrogens in the urine were relatively low, falling from 900 to 200 rat units per day during the week before fetal death occurred, but persisting as usual in some quantity until about the second post-partum day. Estrogens in the serum were low from the beginning of the study and were practically nondemonstrable in specimens studied two and nine days, respectively, before fetal death occurred. Pregnanediol was present in the urine in traces on the sixteenth and thirtieth days before fetal death, but at other times was apparently absent.

The prolactin values were within the normal range, 1,000 to 2,000 rat units per liter for the serum, and 1,000 to 3,000 units for the urine. These findings are in accord with previous observations that estrogen excretion falls much sooner after fetal death than does the prolactin.<sup>3, 35</sup>

The sodium balance was positive for the first week of the study, and then was consistently negative until labor occurred. A slight positive balance then developed for two days, after which the fall was resumed until 14.68 gm. had been lost.

The potassium showed an opposite trend, and its steady but slight retention remained unaffected by the fall in hormones, the death of the fetus or delivery. By the end of the study 11.00 gm. had been gained.



*Comment.*—The loss of sodium in this case began before labor and before fetal death. The only observable trend either in clinical features or laboratory determinations with which it could be correlated was the fall in estrogen and pregnandiol values.

The opposite trend of potassium is difficult to understand. It is perhaps noteworthy that in the other case of toxemia divergence of the curves for the two electrolytes also occurred, but after delivery. In none of the normal cases was this as marked.

#### RELATION OF SODIUM AND POTASSIUM BALANCE TO HORMONE CONCENTRATION IN A NORMAL PATIENT RECEIVING LARGE DOSES OF ESTROGENS

Conditions the reverse of those associated with fetal death should theoretically be producible by the administration of hormones. In this respect two experiments suggest themselves. First, can sodium retention be increased antepartum by adding to the physiologic hormone supply, and, second, can the usual post-partum loss be prevented by artificially maintaining ante-partum levels?

CASE 6.—M. M. (History No. 119853), admitted Feb. 2, 1939. This patient was a twenty-two-year-old girl in her second pregnancy, which had been entirely normal since her last period on May 23, 1938. After being on a measured intake of sodium and potassium for five days, she was given a total of 180,000 rat units of estradiol benzoate\* in six injections on two successive days. There was no evident clinical effect of these injections on the patient. She was spontaneously delivered on June 15 of a six pound, eleven ounce female child after a labor of fourteen hours. The blood loss amounted to 515 c.c.

On each of the first five post-partum days, the patient received two injections of 30,000 rat units each of estradiol benzoate. The breasts failed to enlarge and no milk was available for feeding the baby. Severe afterpains recurred for six days, otherwise the post-partum course was normal.

The nature and quantity of the estrogens injected require some comment. It will be noted that the estradiol benzoate had been standardized in rat units. Therefore the equivalent of about 900,000 international units was injected in the course of forty-eight hours of ante-partum administration and 1,500,000 units during five post-partum days. These amounts appeared comparable to those with which Thorn and Engel obtained their effects on dogs. It must be emphasized, however, that the substance used was the benzoated ester of estradiol, whose effect is slower to develop and more prolonged than is that of the simple hormone. This possibly prolonged effect of the estradiol benzoate should be borne in mind in interpreting the results in this case.

Chart 6 shows that the urinary excretion of estrogen was probably increased for five days during the ante-partum period by these injections and perhaps maintained at a low level for an unusually long period after delivery. The serum estrogen level was unaffected by the estrogen administration and reciprocal effects on the other hormones were not apparent.

Sodium retention in this case was quite marked even before the first estrogen injection, but it continued until term in amounts greater than in any other case. On the fourth post-partum day, there was a loss of sodium, corresponding to that noted in all of the normal cases. Nevertheless, if the entire post-partum period of study is considered, there is evidence of a slight net gain in sodium. This case in which estrogens were administered is the only one in which such a positive balance was present in the post-partum period.

\*The estradiol benzoate was in the form of progynon B, supplied by the Sehering Corporation through the kindness of Dr. Max Gilbert.

9	150/112	129½	2.4	2020	3.14	0.01			3.35	0.14		
8	148/102	129½	2.4	1550	2.40	0.01			2.75	0.14		
7		129½	2.0	1815	2.60	0.01			3.23	0.14		
6	152/110	129½	3.4	1340	2.32	0.01			2.53	0.14		
5	168/138	129½	2.6	1440	2.07	0.10			2.36	0.45		
4	190/120	129½	3.0	1580	2.32	0.10			2.62	0.45		
3	172/124	129½	4.2	490	1.51	0.10			1.53	0.45		
2	150/114	129½	2.0	1830	1.81	0.10			2.10	0.45		
1	164/122	129½	2.0	1620	1.70	0.10			1.85	0.45		
Labor	170/ 94		2.0	1020	0.93	0.10		0.03*	1.73	0.45		0.09*
A.				80	0.28			0.04*	0.22			0.05*
B.				220	0.37			0.06*	0.96			0.03*
C.	146/112											
1	140/ 90		3.0	1220	1.32	0.05		0.11	2.94	0.14		0.03
2	136/ 88		3.0	715	0.89	0.05		0.11	1.81	0.14		0.03
3	132/ 98		2.6	1720	2.17	0.05		0.08	2.06	0.14		0.06
4	140/110		2.6	2550	4.38	0.05		0.08	3.40	0.14		0.06
5	170/110		2.6	2310	3.56	0.05		0.08	2.82	0.14		0.06
6	134/ 96		2.0	2135	2.40	0.02		0.04	2.81	0.12		0.03
7	144/100		1.0	2110	2.41	0.02		0.04	3.10	0.12		0.03
8	120/ 80		1.6	1670	2.27	0.02		0.04	2.76	0.12		0.03
9			1.0	1600	2.44	0.02		0.04	2.67	0.12		0.03
10		120	1.0	1135	1.99	0.02		0.04	2.35	0.12		0.03

\*Blood loss in labor and delivery.

Labor A, From beginning of day until onset of labor.

Labor B, From onset of labor until delivery.

Labor C, From delivery until end of day.

TABLE VI. CLINICAL DATA WITH SODIUM AND POTASSIUM VALUES IN PATIENT M. M. (CASE 6)

DAYS	CLINICAL				SODIUM				POTASSIUM			
	BLOOD PRESSURE	WEIGHT IN POUNDS	PROTEIN-URIA GM./LITER	URINE VOLUME C.C./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY	PLASMA MG. %	URINE GM./DAY	FECES GM./DAY	LOCHIA GM./DAY
23		126½	0	990	300	0.58	0.015		22.0	1.24	0.158	
22		125	0	2180		2.81	0.015			4.04	0.158	
21		124	0	1270		0.73	0.015			1.89	0.158	
20		124	0	1655		1.62	0.063			2.08	0.164	
19	100/ 70	123½	0	1635		1.04	0.063			2.34	0.164	
18	106/ 68	124½	0	1530	308	1.39	0.063		22.1	2.32	0.164	
17	108/ 70	124	0	2160		1.51	0.063			2.01	0.164	
16	106/ 70	124	0	1175	310	0.91	0.063		22.1	1.28	0.164	
15	102/ 68	124½	0	1680	315	1.71	0.063		20.2	2.00	0.164	
14		124	0	2245		2.11	0.020			2.32	0.114	
13	102/ 78	125	0	1205		2.20	0.020			2.33	0.114	
12	92/ 64	125½	0	1425		1.01	0.020			1.69	0.114	
11	96/ 60	125½	0	1660		0.63	0.020		21.1	1.30	0.114	
10	92/ 60	126	0	1335	340	0.60	0.013			1.24	0.050	
9	100/ 68	126	0	1410		0.85	0.013			1.06	0.050	
8	100/ 64	125½	0	1770		1.23	0.013			1.81	0.050	
7	92/ 60	124	0	1270	339	0.99	0.013		25.2	1.44	0.050	
6	92/ 56	125	0	1230	345	1.26	0.013		25.7	1.12	0.050	
5	105/ 70	125	0	1250		1.07	0.107			1.53	0.142	
4	95/ 72	125	0	1070		0.27	0.107			0.53	0.142	

The potassium retention began before the injections were given, was not definitely accelerated by the ante-partum administration of hormone and continued into the post-partum period. It was much more marked than in any other case.

*Comment.*—The apparently increased ante-partum sodium retention and the positive balance on all but one of the early ante-partum days suggest that the administered estrogens actually had a physiologic effect. The variability in different normal cases makes caution essential before any final conclusion. Nevertheless the difference in the graphs of sodium balance in the case with a dying fetus and falling estrogen curve and this one while hormone was being administered is very striking.

The rise in the potassium curve is difficult to explain. It may have been within the limits of the normal potassium retention of late pregnancy. It is, however, interesting to note that Thorn and Engel<sup>42</sup> did find a little decrease in potassium excretion after the injection of estrone and alpha-estradiol into normal male dogs. In this respect the effect of the estrogens may differ from that of the cortical hormone (Thorn, Engel and Eisenberg<sup>43</sup>).

#### PLASMA SODIUM AND POTASSIUM

Numerous studies have been made on the sodium and potassium in the serum of normal and toxemic patients. Most of these indicate that no characteristic changes occur (Krebs and Briggs,<sup>21</sup> Denis and King,<sup>7</sup> Stander, Dunnean and Sisson<sup>36</sup>). Determinations of sodium and potassium were made by us on plasma samples taken at the time blood was drawn for hormone studies (see Tables I to VI). These were made also to determine whether any alterations in the plasma concentrations of these ions developed in relation to changing hormone conditions.

a. *Sodium.*—The average normal figure for plasma sodium has been given by Kramer and Tisdall<sup>20</sup> as 335 mg., with a range in normal pregnancy of 320 to 362 as found by Denis and King and of 286 to 327 by Krebs and Briggs. Rossenbeck<sup>27, 28</sup> has claimed a fall in serum sodium and a rise in chloride ion in normal pregnancy, with these trends increased in "nephropathia" and "eclampsia." After studying a long series of cases Macciotta<sup>25</sup> has recently reported low sodium values early in pregnancy, but almost normal figures near term. He noted also a conspicuous lowering of plasma sodium on the fourth and fifth post-partum days. The figures obtained in the present study are in general within the normal range. A slight drop in serum sodium on the fifth, sixth, and seventh days corresponding perhaps to the sodium excretion at this time is, however, suggested in several cases.

b. *Potassium.*—The normal figures for plasma potassium have been given by Kramer and Tisdall<sup>19</sup> as 17.9 to 21.3 mg. per 100 c.c., by Truszkowski and Zwemer<sup>46</sup> as 16.7 to 23.0 mg. These are figures offered by the originators of certain methods of determination and those reported by students of conditions in pregnancy have shown a wide range (Krebs and Briggs<sup>2</sup>). It has been in general agreed, however, that no characteristic changes in potassium plasma content develop in either normal pregnancy or pre-eclamptic toxemia, although a single report suggests that the rate of change of serum potassium levels after the injection of potassium chloride is abnormal in the toxemic patient (Szűcs<sup>40</sup>).

The average figures for the uncomplicated pregnancies of this study fell within the normal range, but showed wider fluctuations than are reported for nonpregnant persons. The average values were a little higher and the range of fluctuation still greater in the two patients with toxemia. The high values occasionally obtained were perhaps an error dependent on some hemolysis during the drawing of the blood, perhaps to potassium reaching the maternal circulation from disintegrating cells of an infarcted placenta or dead fetus.

## FECAL ESTROGENS

The estrogen eliminated in the feces was also estimated in these cases, since it was felt that a potentially disturbed liver function in toxemia cases might influence the rate of excretion of these substances in the bile. The amounts lost by this route were smaller than had been expected from previous reports and no differences were notable in the different types of cases. Loss of estrogens by this means continued for about three days longer than by the kidneys, the additional period probably corresponding to the time required for the products of biliary excretion to be actually eliminated in the stool.

## DISCUSSION

The studies which have been presented show that in pregnancy and the puerperium sodium is retained during periods of high estrogen concentration and is lost during periods of diminishing hormones. Potassium is not clearly correlated with hormone change and is in general consistently retained both in late pregnancy and the early puerperium.

That the estrogens are not only correlated with, but are at least one of the causes of the sodium retention seems probable. On the other hand the possibility remains that sodium loss and the fall in estrogen concentrations are simply both associated with some other factor, as for example, another glandular or metabolic change.

The curve of pregnandiol excretion closely parallels that of the estrogenic substances. Progesterone is also reported as capable of causing salt retention, so that the corpus luteum hormone of the pregnant woman may also play a part in the production of edema.

The gonadotropic hormone seems less likely to be involved, particularly because it was observed in Case 5 that while the prolactin values remained at about normal levels there was a continuous sodium loss.

The manner in which the estrogens or progesterone may act to prevent sodium excretion can only be guessed at. They may displace sodium into the tissues, prevent its excretion by the kidney, or act through some other gland, as for example the posterior pituitary.

Speculation as to a possible involvement of the adrenal cortex cannot be avoided. In the two cases of toxemia of pregnancy, following delivery in the one and death of fetus of the other, there was a pronounced divergence of the sodium and potassium lines. This could be explained as a return to normal from a previous condition of relatively low potassium and high sodium storage. Such an effect could on theoretical grounds have been produced by hyperactivity of the adrenal cortex.

The relationship of the hormones to the cause of pre-eclampsia toxemia is still evidently a very uncertain one. If the school which believes that sodium is a real causative factor is correct, then the estrogens and perhaps progesterone become a link in the chain of events leading to the appearance of the disease.

Toxemia patients cannot be shown to have an excessive estrogen content of the blood, which by increasing sodium retention might lead to increased edema. It is possible that the low blood and urinary values

3	94/ 78	125½	0	1660	326	2.18	0.107			22.2	2.29	0.142
2	106/ 78	125½	0	1420		0.63	0.107				1.25	0.142
1	106/ 78	125½	0	1325		0.53	0.107				1.11	0.142
Labor	110/ 86	125	0				0.107					
A.				964			0.232	1.13*	24.7			0.906
B.											0.59	0.101
Labor					335	2.08	0.028	0.234	22.8			
C.												
1	85/ 50		Trace	1575	329	0.41	0.028	0.254	25.3		2.41	0.101
2	92/ 58		Trace	1545	325	0.87	0.028	0.254	22.7		2.48	0.101
3			0	1350	322	1.36	0.028	0.127	20.0		2.41	0.101
4			0	1680	337	4.60	0.028	0.127	23.4		2.69	0.101
5	118/ 74		0	1870	335	0.96	0.028	0.127	25.7		2.04	0.101
6	118/ 74		0	1480	319	1.08	0.026	0.206	26.5		1.92	0.485
7		114	0	1435	324	1.95	0.026	0.206	27.6		2.07	0.485
8		113	0	1890	324	2.30	0.026	0.206	23.8		2.73	0.485
9		114	0	1850	305	2.13	0.026	0.140	21.5		3.21	0.123
10		113	0	1705	306	0.57	0.026	0.140	21.3		1.71	0.123
11		112	0	1295	328	0.37	0.026	0.140	20.5		1.34	0.123
12		113	Trace	1550	325	0.21		0.045	20.6		1.57	0.042
13		114	0	1700	338	2.34		0.045	20.1		2.13	0.042
14		114	0	1400	336	1.09		0.045	19.7		1.64	0.042

\*Blood loss at delivery.

Labor A, From beginning of day until onset of labor.

Labor B, From onset of labor until delivery.

Labor C, From delivery until end of 24-hour day.

## DISCUSSION

DR. ARTHUR H. MORSE, NEW HAVEN, CONN.—It is well to consider the experimental work that has preceded the studies here reported. Taylor has referred to the loss of sodium and the retention of potassium in instances of adrenal insufficiency and the reverse of these conditions when cortical hormone is given. In this connection Thorn and Harrop pointed out that the similarity in the chemical structure of corticosterone and the sex hormones indicated the possibility of one or more common physiologic properties, and this prompted the investigation of the possible effect of the sex hormones upon the renal excretion of sodium. Moreover, the prolonged survival of animals adrenalectomized during pregnancy and heat, and the favorable influence of the induction of estrus in adrenalectomized dogs made it appear probable to these investigators that a high concentration of sex hormones is beneficial to adrenalectomized dogs.

Thorn and Harrop found that the injection of 5 mg. of estradiol resulted in a marked and rather prolonged period of decreased sodium excretion in a normal male dog and that this decreased excretion was accompanied by a reduced output of urine. As the effect of the hormone diminished, an increased excretion was noted. Indeed, all the sex hormones so far studied by these authors have displayed some degree of a sodium retaining effect. Estradiol and progesterone proved to be the most active substances in this respect, although pregnandiol was similarly effective.

It appeared to Thorn and Harrop that a possible explanation of the beneficial effect of estrus and pregnancy on the survival of the adrenalectomized bitch might be accounted for on the basis of the salt and water retention induced by the presence of an excess of the sex hormones. Whether this action is direct or mediated through some other endocrine gland is unknown at present.

Later Thorn, Nelson, and Thorn, in a study of the mechanism of edema associated with menstruation, found that the injection of crystalline preparations of estrone, progesterone, pregnandiol, and testosterone induced the retention of sodium, chloride, and water in normal dogs. Balance studies in women demonstrated a retention of sodium, chloride, and water during the intermenstrual as well as the premenstrual phase of the cycle. On the other hand, the onset of menstruation was associated with an increased renal excretion of sodium, chloride and water, while the increased output of estrin at the time of ovulation was associated with a sodium and chloride retention.

Taylor has stated that the greater sodium loss in the puerperium is no doubt due to a disposal of extracellular edema fluid. This has perhaps a parallel in the observations of Zuckerman upon the pigtailed monkey. Zuckerman showed that the process of sexual-skin swelling which occurs in this animal is a physiologically regulated edema. The body weight in the female of the species fluctuates with the phases of the area in question, and when the latter is fully swollen, body weight may be 17 per cent greater than when the skin is inactive. Investigations of daily changes in water metabolism showed that the increase in weight can be largely accounted for by the accumulation and retention of fluid in the sexual-skin area where the water is mainly held. For example, the swollen structure in baboons, when removed at autopsy, may weigh from 10 per cent to 28 per cent of the total body weight. Although some of the water is intracellular, most of the retained fluid appeared to be extracellular, for when the edematous tissue was incised, clear and moderately thick fluid dripped freely from the exposed surfaces. Moreover, when removed at autopsy, frozen, and then sectioned with a knife, the cut surfaces of the tissues were found to be largely made up of crystals of ice.

Zuckerman has shown further that swelling of the sexual skin, which in the pigtailed monkey is present during follicular activity, does not normally occur during the post-ovulation phase of the menstrual cycle. This observation indicates that the progestin produced by the corpus luteum is unable to retain in the tissue in question the water deposited there as a result of estrogenic stimulation in the pre-ovulation phase. A series of experiments carried out on spayed pigtailed macaques which had been first injected with estrone in order to induce the edematous tissue reaction showed that neither testosterone propionate nor cortin was able to prevent

for the estrogens should be taken as an indication of high utilization or failure of the conjugation mechanism and hence imply excessive estrogen effectiveness. On the other hand a perhaps more likely explanation is that in susceptible patients amounts of estrogen normally present in pregnancy will lead to the retention of unusual quantities of sodium.

### CONCLUSIONS

Evidence has been presented to show that certain of the placental hormones, notably the estrogens, are probably factors in the retention of sodium during pregnancy.

These hormones should then be added to the list of contributing factors, such as high sodium intake and lowered plasma proteins, which may predispose to edema in pregnancy.

So far as water and salt retention are related to either the cause or the symptoms of pre-eclamptic toxemia, the estrogens and perhaps the other placental hormones are also factors.

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More recently Richter and Barelare have approached the problem from a different and somewhat unique viewpoint. They studied the nutritional requirements of rats by allowing them to select their own foods. It was found that if presented with a variety of pure substances, such as casein, sucrose, olive oil, sodium chloride, dibasic sodium phosphate, calcium phosphate, calcium lactate, potassium chloride, dried baker's yeast, cod liver oil, wheat germ oil and water, the rats made selections which were conducive to excellent growth and normal reproduction. As soon as the rats became pregnant, however, certain marked differences were noted in the foods they selected. Among the minerals, the most notable alteration observed was a decided increase in the animals' appetite for calcium chloride and sodium chloride. The amount of these substances consumed increased four-fold, whereas other minerals such as potassium chloride were taken in the same quantities as before.

If it be granted that there is an increased affinity of the tissues for sodium in pregnancy, particularly in the toxemias, it is of course important to inquire why. The theme of Taylor's paper is that the estrogenic hormone is probably an important factor. Certain of Taylor's findings surely seem convincing, particularly his results in Cases 4 and 6. In the former, a case of toxemia, the tremendous increase in sodium excretion post partum can only mean that the accumulated concentration of sodium in the tissues of this patient, when suffering from the toxemia, must have been exceedingly high in relation to their concentration in the non-pregnant state. His demonstration in Case 6 that it is possible to maintain a positive sodium balance in the puerperium by administering the estrogenic hormone is a dramatic demonstration that some relationship exists between these two factors, the estrogens and sodium balance. When we come, however, to the question whether the estrogens, through their effect on sodium balance, are responsible for the edema seen in the toxemias of pregnancy, there would seem to be a link missing in the chain. I refer to the fact that in the toxemias, the estrogenic hormone, as is well known, shows abnormally low concentrations both in blood and urine, whereas we would naturally expect, if the above hypothesis is correct, a high one. While this apparent inconsistency does not by any means invalidate Taylor's views, it would seem to require explanation before any *causal* relationship can be postulated between the estrogenic hormone and the edema seen in the toxemias of pregnancy.

DR. WILLIAM J. DIECKMANN, CHICAGO, ILL.—We have been carrying out balance studies for some years, particularly for chlorine, phosphorus, nitrogen, and total salts in the urine. There is undoubtedly a retention of sodium chloride and water in pregnancy which is exaggerated in the pre-eclamptic and eclamptic patient. Which substance is primarily retained we are unable to say at the present time. We had one eclamptic patient whose baby was dead for ten days, but there was no release of sodium, chlorine, or water until the expulsion of the fetus. This is contrary to the findings in one of Taylor's cases.

I wish to report some unpublished data of F. Koch and A. T. Kenyon of other departments of our University. They have complete balance studies for a period of four weeks obtained on two normal males and two normal females. These individuals ate the same food three times a day and for a period of seven days in the middle of the study were given 25 mg. of testosterone daily. There was a significant retention of total nitrogen, inorganic phosphorus, potassium, chlorine, and sodium. Likewise the weight increased. Shortly after the stoppage of the male hormone, there was a negative balance for these various substances. This work fits in very well with the observations made by Taylor.

DR. TAYLOR (closing).—Several of the speakers, particularly Morse, have mentioned other clinical effects that might be produced by the sodium-retaining action of the estrogens. He referred to the increase in weight and the apparent retention of fluid in the sexual-skin of monkeys. The great breast swelling which occurs in some women before menstruation is perhaps merely a storage of fluid in that region, and it is entirely possible that that is due to the premenstrual hormone conditions.

the normal excretion of sexual-skin water once the estrogenic stimulation had ceased. On the other hand, the injection of pitressin at short intervals did delay the subsidence of the swelling.

Although the part played by the hormones in pregnancy is not understood, investigations in the monkey carried out by my laboratory associate, Prof. Gertrude van Wagenen, throw some light on certain phases of the hormonal activity of the placenta. One of these studies relates to the possible hormonal activity of placental tissue left in the uterus following the abdominal delivery of the fetus. Earlier investigations in the mouse and guinea pig have shown that if the fetus is removed but the placenta is allowed to remain in situ, the animal in which this organ is retained persists in its habitus of pregnancy until the afterbirth is delivered spontaneously at the termination of a normal period of gestation. Since gestation in the rodents is comparatively short, a study of the rôle of the placenta in the absence of the fetus, and of placental hormonal activity is more favorably investigated in the monkey in which the duration of gestation is 168 days. In this study van Wagenen removed only the fetus by abdominal hysterotomy. Such a procedure in the monkey gives some technical difficulty since the placenta consists of a primary and a secondary lobe joined by large vessels. Moreover, in early gestation the comparatively heavy musculature of the primate uterus obscures the sites of placental implantation and, if care is not exercised during the operative procedure, uterine contractions are likely to detach the vascular structure. In the group of animals under observation the placenta was retained as long as ninety days without giving rise to external bleeding or to other untoward symptoms. It was then expelled at the termination of the period previously estimated in the case of each monkey for the delivery of a fully matured offspring. The maternal gain in weight occurring during early gestation and the intensification of the sexual-skin coloration persisted until the expulsion of the placenta. Subsequent to the extrusion of this organ there was a loss in body weight exceeding that of the shed placenta and a rapid fading of the coloration of the sexual skin. These findings, together with the fact that lactation was not initiated following the removal of the fetus, suggest that in the monkey the hormonal relationships of pregnancy continue in the presence of the placenta and the absence of the fetus.

Taylor has shown that during pregnancy there is a retention of sodium similar to the retention which Thorn, Nelson and Thorn noted during the intermenstrual and premenstrual phases of the cycle, but that following delivery there is an increased excretion of sodium similar to the increased renal excretion of sodium, chloride and water associated with the onset of menstruation. Finally, he has taken a conservative and, I believe, a wise viewpoint when he indicates that the possible relationship of the estrogenic hormones to the causation of the toxemias is at present not clear. While this possibility must be held in mind, our knowledge of the various hormones and of the interrelationship of the various endocrine glands is still too meager to hazard any definite statement upon this point. On the other hand, investigations of the type just reported will go far in clearing at least some of these vexing problems.

DR. NICHOLSON J. EASTMAN, BALTIMORE, MD.—Evidence of various types is making it clear that the edema, so frequently seen in the toxemias of pregnancy, is conditioned in part at least by an increased avidity of the tissues for sodium chloride. Some years ago Ropp carried out the following experiment: After feeding 5 gm. of sodium chloride to various types of patients, under carefully controlled conditions, he studied the resultant changes in the chlorides of the blood and urine, and from this was able to deduce the fate of the ingested salt. Even in normal pregnancy he found a greater affinity of the tissues for sodium chloride, the blood chlorides augmenting only slightly after feeding the salt, while the urinary excretion was delayed. In toxemias with edema, this was still more marked, so that the ingestion of sodium chloride showed no effect on either the blood or urinary chlorides, all of the ingested salt being held by the tissues. Finally, Ropp analyzed edema fluid and showed that after ingestion of salt by edematous pregnant women, the sodium chloride concentration of this fluid was increased.

## GONADOTROPIC HORMONE

The anterior pituitary hormone content of the blood was determined in 66 patients. Of these, 20 were in the premenopausal, 24 in the

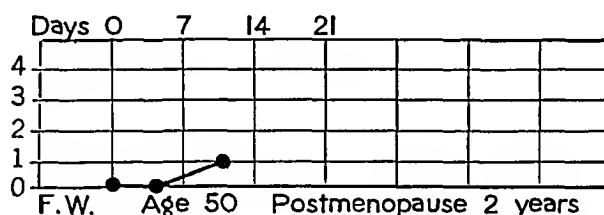
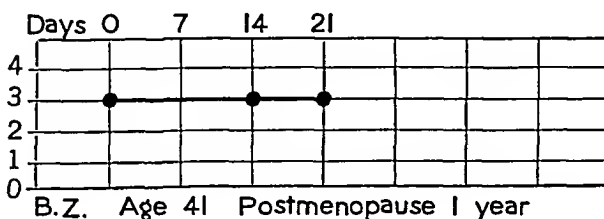
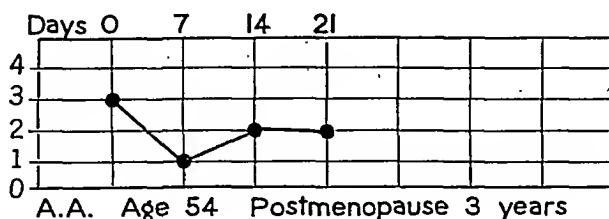


Fig. 1.—Estrogen in the blood of postmenopausal women.

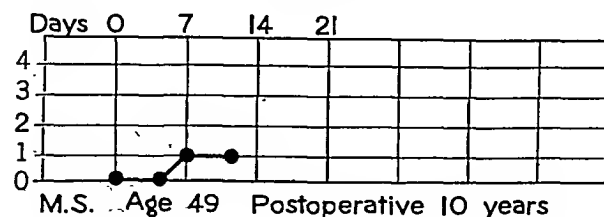
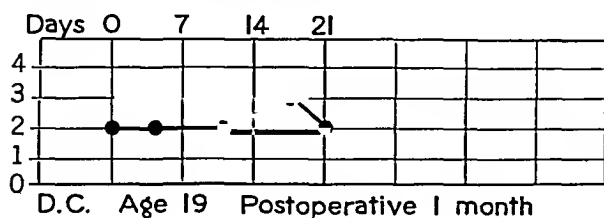
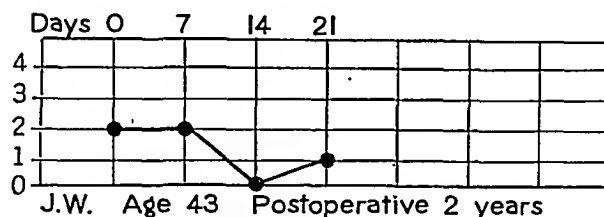


Fig. 2.—Estrogen in the blood of women following castration.

Eastman has put his finger on a very weak point in the hypothesis that the excessive edema in toxemia is an estrogen effect. Most studies show in fact that the estrogenic curves are lower in toxemic patients than in normal pregnancy. This objection can be explained away on various theoretical grounds. The simplest one is to suggest that the low estrogen excretion is evidence of greater utilization by the tissues. This is pure theory, however, and cannot be assigned any importance at present.

Dieckmann cited a case in which the electrolyte changes did not occur in a case of fetal death until after the expulsion of the fetus. It is highly probable that the placenta is differently affected in its hormone activity under various conditions of fetal death. Different reactions on electrolyte behavior would also be expected.

I want it perfectly clear that this is not offered as any new theory of the cause of pre-eclamptic toxemia. It is essentially a study of the cause of what Eastman has described as the increased avidity of the tissues in pregnant women for sodium. I do think, however, that the estrogens and progesterone are the most likely candidates at present to be the cause of this increased avidity of the tissues in pregnancy for sodium, chlorides, and water.

1. *Sedatives*.—In our earlier studies the blood was examined at weekly intervals, and during this period of some four or five weeks the patients were given a mild sedative, such as  $\frac{1}{4}$  gr. of phenobarbital every four hours. As might be anticipated, no effect was observed on the concentration of the hormone in the blood. It is interesting, however, that the results bear out the concept that severe climacteric symptoms are associated with increased amounts of anterior lobe hormone. Of 24 patients studied in this manner, 18 gave consistently positive tests while under observation. Ten, or 55 per cent, reported definite improvement from the use of sedation, while 8 reported no change. On the other hand, of 6 patients with negative tests, all were improved to the point that no other method of treatment was necessary.

2. *Estrogenic Hormone*.—The intensive treatment with estrogenic hormones of climacteric patients, resulting in a disappearance of gonadotropic substances in the urine, has been reported by a few observers, notably Albright<sup>7</sup> and Frank and his co-workers.<sup>8</sup> Although our series is small (Table IV), it definitely points to the fact that the general improvement of these patients is not necessarily dependent on the disappearance of the hormone from the blood. The amount of estrogen used in this study, with one exception, was 60,000 I.U. given in divided doses over a period of two weeks. This may be considered inadequate on the basis of the work of Frank

TABLE IV. EFFECT OF ESTROGEN THERAPY ON THE GONADOTROPIC HORMONE CONTENT OF THE BLOOD

PATIENT	TESTS BEFORE TREATMENT				ESTROGEN THERAPY	TESTS AFTER TREATMENT				CLINICAL RESULT
L. A.		+	+	+	Amniotin 60,000 I.U.	0	0	0	0	Not improved
S. R.		+	+	+	Progynon-B 30,000 I.U.	?	0			Improved
A.	0	0	0	0	Progynon-B 60,000 I.U.	0	+	0		Doubtful
H. P.	0	0	0	0	Amniotin 60,000 I.U. repeated— check	0	0	0	0	Improved
R. C.	0	0	0	0	Progynon-B 60,000 I.U.	0	0	0		Improved
J. W.		+	+	+	Progynon-B	+	+			Slight improvement
L. H.		+	+	+	Progynon-B 60,000 I.U.	+	+	?		Improved
G. J.			+	+	Progynon-B 60,000 I.U.	+	+			Improved
F. E.			+	+	Amniotin 60,000 I.U.	+	+			Improved

and others,<sup>8</sup> but nevertheless 6 of the 9 patients were clinically improved and demanded no further treatment. Of the 9, positive tests before treatment and negative afterward were observed in only two instances. One of these patients was improved, and one was not. In 3 cases, tests for the gonadotropic hormone were negative both before and after treatment. In 4 cases, the examination of the blood gave positive tests both before and after the use of estrogenic hormone and all reported relief from distressing symptoms.

3. *X-Irradiation of Hypophyseal Area*.—The treatment of menstrual disorders and climacteric symptoms by x-irradiation of the skull has been advocated for many years. A very carefully controlled series of patients was reported from this clinic a few years ago (Newell and Pettit<sup>9</sup>). Since a large proportion of women were improved, it seemed of importance to determine whether this was accomplished by diminishing the amount of anterior lobe hormone in the blood. The roentgen technique employed has been described by Newell and Pettit,<sup>9</sup> but in this study much larger dosages were employed at times, and treatment was directed to the top and

postmenopausal, and 22 in the castrate group. A total of 173 tests was conducted.

The results are given in Table III, and it will be apparent at once that a definite relationship exists between the presence or absence of the hormone and the severity of the hot flushes. This is shown, not only in the total figures for the entire series, but also in each individual group.

TABLE III. GONADOTROPIC HORMONE IN THE BLOOD OF CLIMACTERIC WOMEN AND CASTRATES

GRADE	PREMENOPAUSAL				POSTMENOPAUSAL			
	NEGATIVE		POSITIVE		NEGATIVE		POSITIVE	
	NO.	%	NO.	%	NO.	%	NO.	%
I	9	70	4	30	6	50	6	50
II	2	29	5	71	1	15	6	85
III					0	0	4	100
IV					0	0	1	100
Total	11		9		7		17	

GRADE	CASTRATES				TOTAL			
	NEGATIVE		POSITIVE		NEGATIVE		POSITIVE	
	NO.	%	NO.	%	NO.	%	NO.	%
I	0	0	7	100	15	47	17	53
II	2	28	5	72	5	24	16	76
III	0	0	4	100	0	0	8	100
IV	0	0	4	100	0	0	5	100
Total	2		20		20		46	

In the first place, the highest incidence of positive tests occurred in the groups with the greatest number of patients of Grades II to IV. Conversely, the more patients in Grade I, the fewer the positive tests. For instance, in the premenopausal group, 64 per cent of the women fell in Grade I, and only 9 out of 20 gave positive tests, while in the postmenopausal group the incidence of Grade I was 43 per cent and positive results were found in 17 out of 24 women. Finally, only 25 per cent of the castrates belonged to Grade I and 20 out of 22 consistently showed the presence of increased amounts of anterior lobe gonadotropic hormone in the blood.

Second, an increasing incidence in the number of positive tests is seen when the patients are graded according to the number of hot flushes occurring each day, an observation which holds for all three groups. A total of all the patients shows that positive tests were found in 53 per cent of Grade I, 76 per cent of Grade II, and 100 per cent of Grades III and IV.

#### EFFECT OF TREATMENT ON HORMONE IN BLOOD

Since a close relationship exists between the presence of unduly large amounts of anterior lobe gonadotropic substances in the blood and the severity of climacteric symptoms, an attempt was made to determine the influence of various methods of therapy on the hormone level. Three small groups were available for this purpose.

was first made by one of us (Fluhmann<sup>12</sup>). Zondek<sup>13</sup> later described the endocrine changes of the climacteric as occurring in a definite order, stating that his hormone studies of blood and urine indicated three stages: first, a period of excessive estrogen production; second, an absence of estrogen; and third, a hypersecretion of gonadotropic hormone with a total absence of estrogen. This statement, not supported by protocols or detailed experimental evidence, has been widely quoted, nevertheless, in medical literature. It never has been substantiated, and an analysis of our own observations from patient to patient fails to bring corroboration. In a noteworthy contribution, Albright<sup>7</sup> drew attention to overproduction of gonadotropic substance and the occurrence of hot flashes. He demonstrated that persistent estrogenic therapy which diminished the excessive excretion of gonadotropic factors, usually brought about a general improvement of the patient. Frank and others<sup>8</sup> following an extensive investigation, reached essentially the same conclusion.

It is difficult to compare our findings directly with those of investigators who base their endocrine tests on biologic changes in laboratory animals injected with material which they obtain from blood or urine by a prolonged chemical extraction. However, our studies lead us to believe that there is a distinct relationship between the severity of climacteric symptoms and the occurrence of abnormal quantities of gonadotropic anterior lobe hormone in the blood. A further analysis of our results makes us feel that we are not dealing with a "cause and effect" problem. Severe symptoms and positive blood tests appear concurrently, but the findings in women treated in various ways indicate that clinical improvement may be obtained while large amounts of the hormone are still present in the blood. It is known also that excessive amounts of gonadotropic factors are excreted in the urine many years after climacteric symptoms have disappeared. It seems more logical, therefore, to infer that the symptoms and the overproduction of the hormone both result from a common basic cause rather than that the activity of the anterior hypophysis is directly responsible for the complaints characteristic of the climacteric epoch. If this is so, the value of routine employment of blood or urine tests as a therapeutic index becomes doubtful. However, because of the well-recognized effect of autosuggestion in the treatment of these patients and the difficulty of correctly evaluating clinical results, it is hard to give a precise answer.

#### CONCLUSIONS

Examination of the blood of climacteric women and castrates revealed that, in general, failing or absent ovarian function is not associated with a complete disappearance of substances having estrogenic properties when injected into spayed rodents. The hormone may be detected at cyclic intervals or it may be constant, but no relationship between climacteric symptoms and its absence or presence could be established.

The presence of excessive amounts of a gonadotropic substance probably of anterior hypophysial origin was found in the blood of women

TABLE V. X-IRRADIATION OF THE SKULL AND ITS EFFECT ON THE GONADOTROPIC HORMONE CONTENT OF THE BLOOD

PATIENT	GRADE	TESTS BEFORE TREATMENT			X-RAY DOSAGE	TESTS AFTER TREATMENT				CLINICAL RESULT
		+	0	0						
E. S.	II	+	0	0	3200 r.	0	0	0		Improved
A. O.	II	0	0	0	770 r.	0	0	0	0	Improved
B. W.	I		0	0	770 r.	0	0			Improved
S. H.	II	+	+	+	3200 r.	+	+	+	+	Improved
V. Z.	IV		+	+	4400 r.	+	+	+		Improved
H. K.	III		+	+	770 r.	+	+	+		Not improved
E. G.	I	+	+	+	1600 r.	+	+			Doubtful

back of the skull as well as over each temple. An extensive epilation occurred on two occasions. It is seen from Table V that in 3 patients tests for gonadotropic hormone in the blood were negative both before and after treatment, and all three reported marked diminution or absence of hot flushes. In 4 instances, the tests remained positive after irradiation, and 2 patients were improved, 1 reported no change, and in 1 the result was doubtful.

### DISCUSSION

Since estrogen was demonstrable in the blood of such a large proportion of our patients, it appears that the lack of this hormone is not the primary factor concerned in the production of climacteric symptoms. However, our findings open important questions regarding the production and function of the estrogens and their relation to ovarian activity.\*

Estrogenic hormones are not demonstrable in the blood during early life. They first make their appearance at about the age of eight years, when the secondary sexual characters begin to develop (Fluhmann<sup>3</sup>). In adult life, they are found at cyclic intervals and generally accompany certain specific events of the menstrual cycle. These observations point to a close relationship with the function of the ovaries, but leave us in the dark as to the significance of the estrogens in the absence of the gonads. They must have an extragonadal origin, and the adrenals have been suggested as the probable organ responsible for their production (Parkes<sup>11</sup>). However, another unexplained observation in castrates and in patients after the menopause is the atrophy of the accessory sexual organs which occurs in spite of the presence of the hormone. It is possible that the ovaries do not produce estrogenic substances at all, but merely utilize them or change them into a more active form which can act on the uterus and vagina. A second possibility is that there is only *one* true "ovarian hormone" and that the substances found in the blood after the gonads are removed are by-products of cholesterol metabolism which are capable of inducing changes in the rodent vagina but not of maintaining the integrity of the human accessory genital organs.

The association of climacteric symptoms with an increase of gonadotropic substance in the blood or urine is not a new observation. It

\*Since our studies were made in patients with symptoms, the criticism may be advanced that they cannot be considered as representing normal climacteric women. In a recent report, however, Shute<sup>10</sup> found that estrogen was demonstrable in the blood of a large percentage of postmenopausal patients, and that the presence or absence of symptoms did not alter the incidence of positive tests for the hormone.



# EXPERIMENTAL BIOLOGICALLY ACTIVE OVARIAN TUMORS IN MICE\*

## HISTOGENESIS AND RELATIONSHIP TO SIMILAR HUMAN OVARIAN TUMORS

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OVARIAN tumors possessing biologic activity have been produced by the roentgen irradiation of mice. Such tumors exhibit a striking similarity to those human ovarian neoplasms which produce estrogenic effects; namely, the granulosa cell tumor and its more luteinized variations, and the theca cell tumor. Much has been written in the last decade concerning both the structure and origin of these human ovarian tumors and their hormonal significance. There is still, however, considerable speculation in regard to their histogenesis and the relationship they bear to each other.

Studies of serial sections of the ovaries of irradiated mice have made available to us a material from which certain conclusions can be drawn regarding the development of these neoplasms. This experimental investigation may also afford a key to a more fruitful consideration of their counterparts in the human being.

### METHODS AND MATERIALS

All the experiments were carried out with white, female mice of an inbred, homogeneous stock. At the time of irradiation the mice were approximately five to six weeks old (puberty). Two hundred mice were irradiated while 35 were kept as controls. Each mouse received 200 r., measured in air, in a single dose. The irradiation factors were 180 kv., 8 ma., 50 cm. distance, 0.5 mm. Cu. filtration for one group and 200 kv., 20 ma., 50 cm. distance, 1.0 mm. Cu. filtration for a second group.†

The incidence of ovarian tumors subsequent to roentgen radiation has already been charted for several strains of white mice by Furth and Furth.<sup>8</sup> We were primarily interested in the histogenesis of these tumors. Therefore, most of the mice which died spontaneously were ignored in this study. It was felt desirable to use mice which could be autopsied immediately on being killed in order to insure the minimum of post-mortem change. Complete autopsies were done.

One hundred seventeen mice were studied in this series. For the early changes after irradiation at least one mouse was killed and examined each day during the first seven weeks. There were 55 mice in this group. During the period from seven weeks to ten months, 24 mice were examined at intervals. And finally, during the period from ten to fifteen months, 38 mice were similarly examined.

Of the 38 mice in the last group 22 exhibited ovarian tumors of various types.

\*Read at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, Va., May 22 to 24, 1939.

†The irradiation was carried out in the Department of Radiotherapy of The Mount Sinai Hospital through the kindness of Dr. William Farris and with the cooperation of Dr. Louis Zaretzki.

of the climacteric age and after castration. It bears a distinct relationship to the severity of so-called climacteric symptoms. Clinical improvement of such patients was observed following treatment with sedatives, estrogen, or X-irradiation of the skull, while unduly large amounts of gonadotropic substances were consistently demonstrable in the blood.

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# DISCUSSION

DR. EMIL NOVAK, BALTIMORE, MD.—Fluhmann has made reference to the early work of Zondek on the hormone conditions of the menopause. You will recall that Zondek spoke of three phases, viz., hyperfolliculinism, hypofolliculinism, and polyprolanism, the last-named persisting for many years after the menopause. This view of the endocrine sequence of events at the menopause has had to be modified in various ways, and there are no doubt individual differences in different women. The frequent persistence of estrogen for many years after the menopause is now well established. Fluhmann has shown that this persisting estrogenic hormone may exhibit cyclical variations, and this may have a bearing upon the not infrequently periodic nature of vasomotor exacerbations in the menopausal years.

While the postmenopausal persistence of gonadotropic principles is well recognized, it seems clear that this excess cannot in itself cause the menopausal symptoms, for it commonly persists long after the disappearance of such symptoms. It is not surprising, therefore, that Fluhmann finds that estrogenic therapy frequently relieves the symptoms, even though the gonadotropic hormone still persists. In a small number of cases, Bennett in our laboratory has found that even the implantation of estrogenic pellets of considerable strength will not always bring about disappearance of the gonadotropic hormone, though the symptoms are relieved.

Studies of this sort indicate to my mind that imbalance of opposed hormones is more frequently the cause of clinical symptoms than is mere quantitative excess of one hormone. This point can be illustrated in various ways. A good example is primary dysmenorrhea, which so often begins not at puberty, but a short time later, i.e., when ovulation and corpus luteum formation begin. Before this in many girls only estrogen is present, but dysmenorrhea is not noted until the imbalance between this and the corpus luteum becomes operative. Again, dysmenorrhea is rarely seen in the functional bleeding of middle life, when again estrogen is present without progesterone. And other examples might be adduced.

losa cells is noted, examination of serial sections discloses a fairly well-preserved ovum. This would seem to indicate a delay in follicle destruction rather than a proliferative effect due to x-ray. Though some necrosis of granulosa cells occurs early, follicular atresia is not complete until about the seventh week. "Anovular follicles" within the cortex of the ovary at this stage refer to the single-layered follicles in which the ovum has disintegrated, leaving a circular or folliculoid arrangement of cells. They are of interest especially because some of them may persist long after the larger follicles have disappeared. They show no evidence of growth, however, and their role is not of significance.

The theca interna is not destroyed by the irradiation. It begins to proliferate about some of the follicles as early as the first week. The theca interna is represented by several layers of plump, epithelioid cells arranged in a circumferential manner around the degenerating follicle, and merges indistinctly with the surrounding parenchyma. Their nuclei are large, ovoid and vesicular, with occasional mitotic figures. It is of critical importance that the granulosa cells do not participate in this proliferation. Occasionally, areas are found in which proliferating theca interna cells merge imperceptibly with the surrounding tissue. Moreover, the line of demarcation between granulosa and theca cells may be obscure. It is thus possible to mistake proliferating theca cells for persisting and proliferating granulosa cells. Serial sections disclose, however, that this picture is produced by tangential section through the proliferating theca about a degenerating follicle, since deeper sections reveal a distinct demarcation between granulosa and theca (Fig. 2). Further contrast between theca and granulosa cells is made possible by differential stains (Mallory and Masson). These bring out the fine connective tissue strands among the theca interna cells and their absence among the granulosa cells.

The interfollicular tissue of the ovary begins to show evidence of change during the third and fourth weeks after irradiation. At this time one can detect an increase in the size of the parenchymal cells and a tendency to be separated into rounded groups or elongated cords by thin strands of connective tissue. The cytoplasm acquires a foamy appearance, and the nuclei appear larger, paler, rounder, and more vesicular. With succeeding weeks this luteinization of the parenchyma becomes more apparent, progressing as the follicles show increasing degeneration. The proliferating theca interna likewise shows evidence of slight luteinization and tends to become indistinguishable from the surrounding tissue.

Corpora lutea, when present, appear to be well preserved. In one instance, fifty-five days after radiation, section of an ovary showed a complete disappearance of all follicles, slight but diffuse luteinization of the parenchyma and the persistence of a well-preserved corpus luteum. Although it is possible that ovulation may occur a few days after irradiation,<sup>20</sup> it does not occur at this late date. The corpus luteum differs from the remainder of the ovary in that it consists of a single, rounded, well-demarcated mass, in which the individual cells show round, uniform nuclei and more homogeneous, acidophilic cytoplasm.

## LITERATURE

The effects of x-rays upon the ovaries of mice were described in detail by Brambell, Parkes and Fielding,<sup>1-5, 19, 20</sup> in a series of studies beginning in 1927. Irradiation of immature female mice resulted in primary degeneration of the ova, followed by complete disintegration of the follicle structure. The interfollicular tissue was replaced by cords of luteallike cells which were interpreted as having originated from proliferations of the germinal or surface epithelium. A second proliferation was described in some cases in which a folliculoid arrangement of cells was noted. In mature mice, the ova were likewise destroyed but no post-irradiation proliferations from the germinal epithelium were observed. Instead, the tissue composing the sterilized ovaries after two and one-half months was described as having been derived from persistent and growing membrana granulosa cells and the interfollicular elements of the ovarian cortex.

The fat-containing, luteallike cells which finally replace the ovarian parenchyma in irradiated mice are of particular interest and will be fully considered below.

It was further found that in irradiated immature mice that reached maturity, the estrus cycle was not suppressed. In other words, even after destruction of the follicle apparatus, sufficient estrogenic hormone was elaborated to produce extra-ovarian changes of estrus. When, however, a bilateral oophorectomy was performed, estrus ceased, indicating that the parenchyma of the ovary was responsible for the production of the estrogenic effect.

Furth and Furth<sup>8</sup> found while studying the effects of x-rays that the incidence of ovarian tumors in irradiated mice kept to senility was 15 times that in control stocks. In an analysis of these neoplasms by Furth and Butterworth<sup>9</sup> two main types were evident: (1) Tubular adenomas, arising by proliferations of the surface epithelium in the form of epithelial canals, and (2) granulosa cell tumors, derived from the cell nests formed from normal follicles following degeneration of the ova. Traut and Butterworth<sup>23</sup> also suggested that these granulosa cell neoplasms were derived from surviving granulosa cells in the x-rayed mice.

## HISTOLOGIC CHANGES IN MOUSE OVARY FOLLOWING IRRADIATION

Following irradiation of mature mice the histologic changes noted within the ovaries pursue a definite pattern. Arbitrarily, these changes may be divided into three stages, each of which presents characteristic features. It must be emphasized, however, that they are not sharply demarcated but are continuous one into the other. A résumé of these postirradiation effects is presented for a better understanding of the evolution of the tumor growths.

## STAGE OF FOLLICLE DESTRUCTION

The surface epithelium shows no changes during the early months. It persists as a single layer of cuboidal cells without evidence of proliferation. The tunica albuginea likewise plays no active role, appearing as a thin, compressed, fibrous sheath.

All primary oocytes show evidence of degeneration within the first two days after irradiation. The normal cell structure of these ova is quickly effaced, leaving only remnants of a shrunken, collapsed zona pellucida. Though eventually absorbed, these degenerated remnants persist for many weeks, their detection being especially apparent with the Mallory stain. The ova within the medium-sized and larger follicles show greater resistance. Some degree of degeneration is, however, apparent in all of them by the second week.

Degeneration within the granulosa cells of the follicles progresses at a slower rate. Greater follicle destruction is noted where the ovum has previously been affected. Wherever mitotic activity among the granu-

## STAGE OF LUTEINIZATION

By the sixth or seventh week after irradiation, the ovaries present a picture of almost complete luteinization (Fig. 2*B*). The entire ovary is replaced by a diffuse mass of enlarged polygonal or rounded cells with distinct, vesicular nuclei, and abundant, foamy cytoplasm. These are arranged into irregular groups by thin strands of connective tissue. The only residue of the follicle system are scattered, small, cystic spaces, containing crumpled remnants of zona pellucida. Although in the normal mouse ovary the bulk of tissue is made up of follicular structures, the luteinized ovaries are not smaller than normal. The space previously occupied by the follicles is compensated for by the enlargement of the parenchymal and theca cells through luteinization. Although

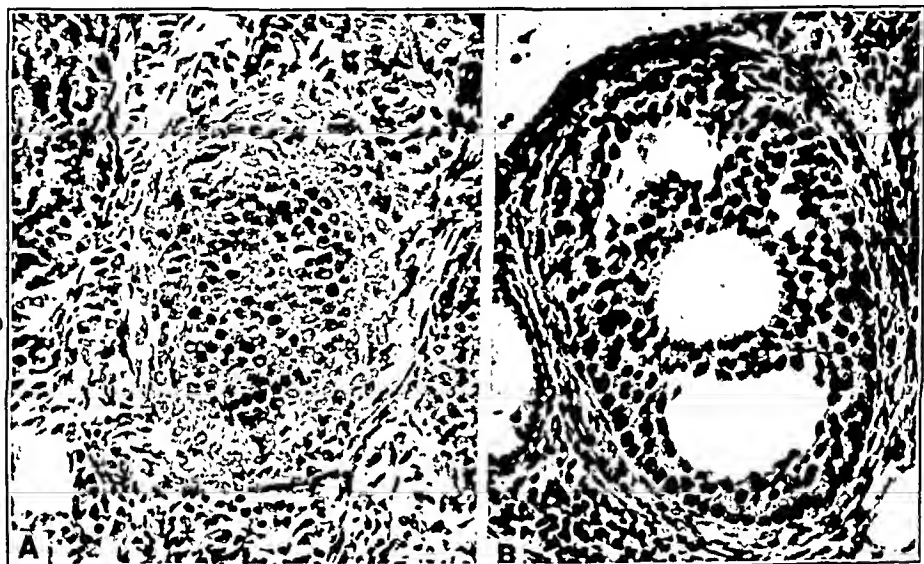


Fig. 2.—Ovary four days after irradiation. *A*, Tangential section through periphery of follicle showing proliferation of granulosa and theca interna cells suggesting the merging of both with the parenchyma. *B*, Serial section through same structure at deeper level shows, however, distinct demarcation between granulosa and theca interna and parenchyma.

proliferation of the luteinized cells is not conspicuous, that such did occur is indicated by the presence of occasional mitotic figures. At the periphery of the ovary the surface epithelium and tunica albuginea appear unchanged. In the outer cortex an occasional folliculoid arrangement of parenchymal cells is noted together with the previously mentioned inactive, "anovular follicles." Ovaries examined during the third, fourth, and fifth months show little change beyond variations in the quantity of luteinization and evidence of partial degeneration of small groups of luteinized cells. The excessively large, foamy, lutein cells may represent evidence of functional exhaustion, comparable to that seen in the human corpus luteum. It is to be emphasized that the uterine mucosa in these cases shows proliferation. The vaginal epithelium exhibits good layering, cornification and mucification. These findings are in agreement with the observations of Parkes<sup>20</sup> who found that in x-rayed mice estrus phenomena could be demonstrated.

To recapitulate, then, the ovaries of mice x-rayed at puberty show definite changes during the first six or seven weeks (Fig. 1A). The surface epithelium and tunica albuginea appear unaffected. The primary oocytes and then the ova of large follicles are quickly destroyed.

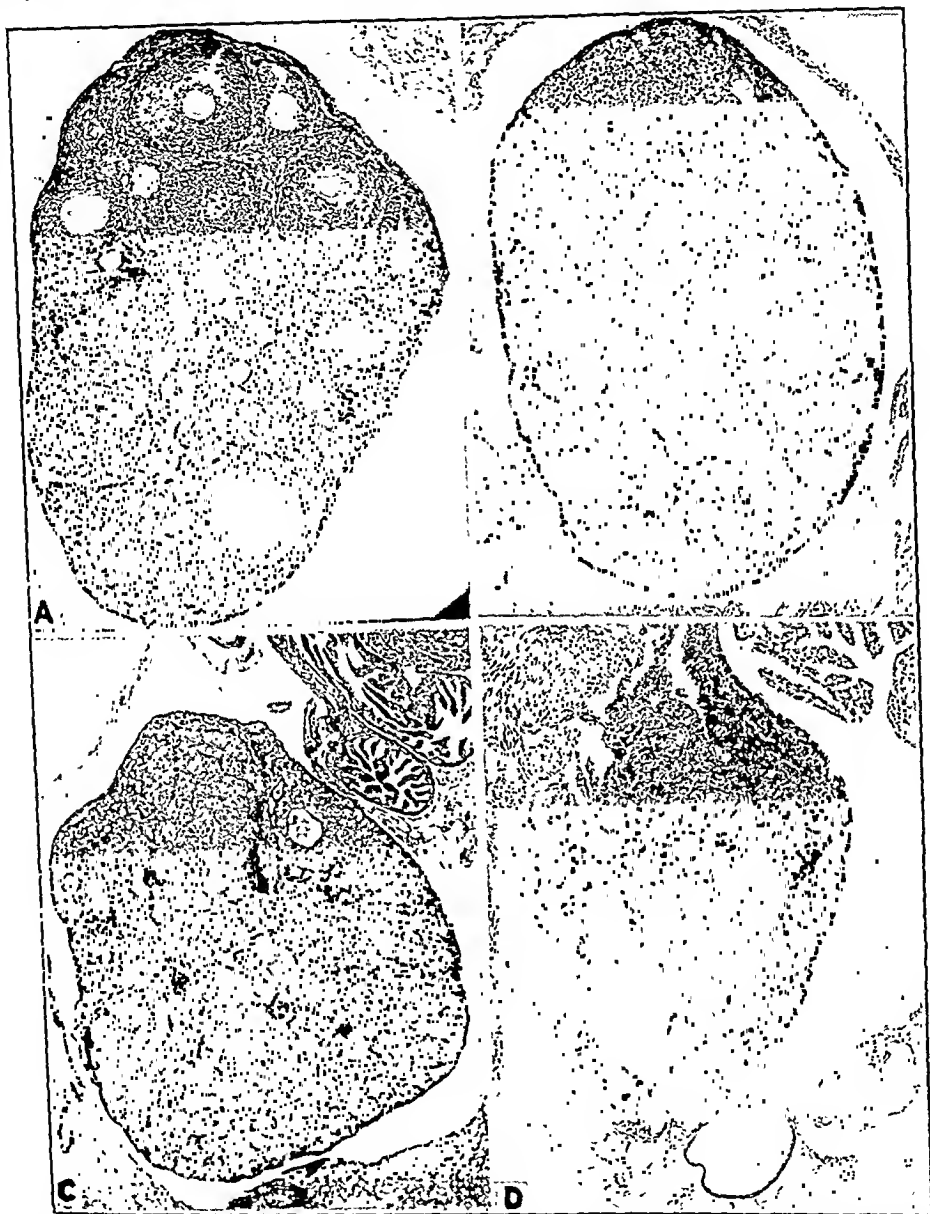


Fig. 1.—Mouse ovaries. Postirradiation changes. A, Stage of follicle destruction. B, Stage of luteinization. C, Stage of tubular downgrowth from surface epithelium. D, Ultimate atrophy of ovary and partial replacement by downgrowing surface epithelium.

The granulosa cells degenerate progressively but more slowly. The theca interna proliferates and along with the interfollicular parenchyma receives a luteinizing stimulus. Corpora lutea are apparently not destroyed and perhaps persist because of the same luteinizing stimulus which affects the parenchyma.

The uterus and uterine horns were moderately enlarged. A vaginal smear taken several days before death showed an estrogenic effect.

On microscopic examination the tumor was composed of cell masses and thick cell cords separated by delicate connective tissue and blood vessels. Most of the cells had an epithelial appearance and resembled the granulosa cells of the normal follicle. The nuclei were mainly small and dark. The cytoplasm was moderate in amount and basophilic or neutrophilic in staining reaction. The cytoplasm was finely vacuolated and contained fat which was doubly refractile through the polariscope. Mitoses were frequent; the tumor appeared to be actively proliferating.

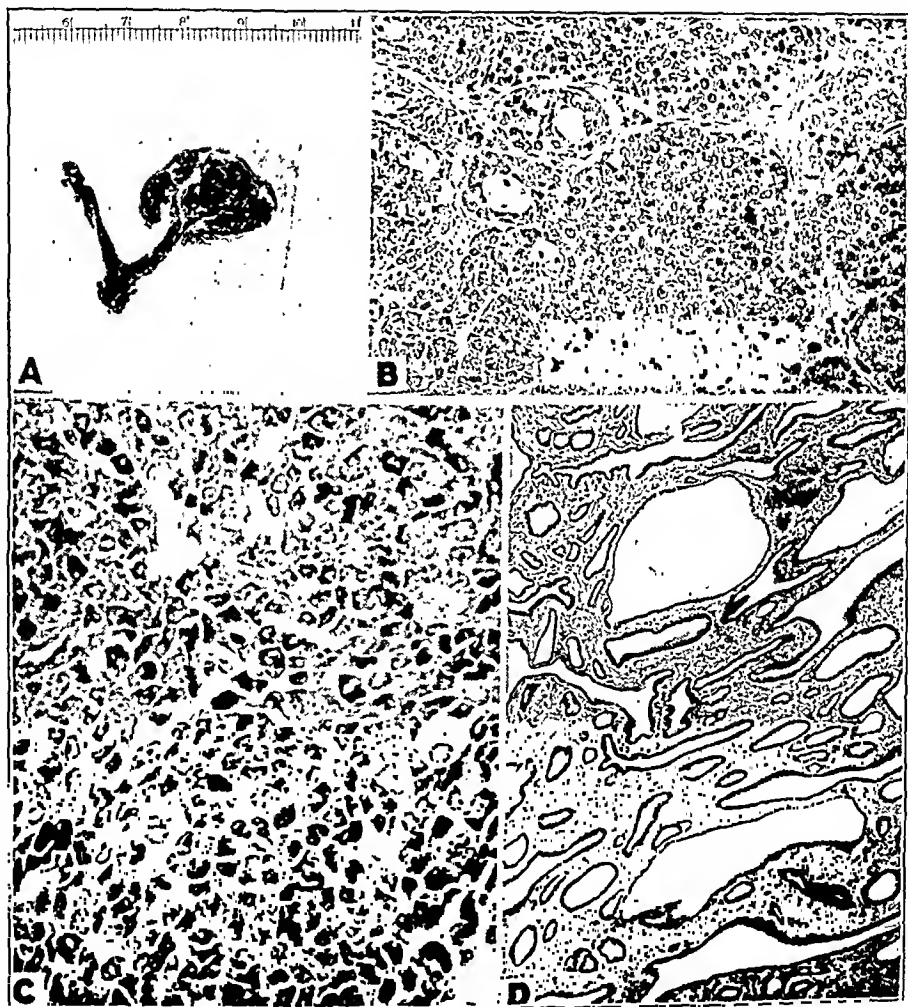


Fig. 3.—Mouse 7-8. Parenchymal lutein tumor of the granulosa cell type. A, Gross appearance of tumor in left ovary. Enlargement of uterine horns. B, Microscopic appearance of tumor (low power). C, Same (high power) showing resemblance of cells to those of granulosa. Several mitotic figures seen. D, Cystic hyperplasia of uterine endometrium.

In some areas the cells were larger, more elongated, and had more vesicular nuclei. These cells resembled more the theca interna cell of the normal ovary. Many cells were much larger and more irregular with hyperchromatic nuclei and even with atypical mitoses (tripolar). In some cells the cytoplasm appeared quite foamy, giving the impression of more marked luteinization. The uterine endometrium showed cystic hyperplasia. The vaginal epithelium showed good layering, cornification and mucification.

## STAGE OF PROLIFERATION OF THE SURFACE EPITHELIUM

After the sixth month, an additional phenomenon is noted in practically all cases. The surface epithelium becomes more columnar and shows evidences of proliferation (Fig. 1C). Numerous small tubular downgrowths penetrate the cortex of the ovary. Though at first confined to a small crescent or thin layer at the periphery, in the older mice this surface proliferation becomes more conspicuous. The gland-like downgrowths are often convoluted so that an adenomatous picture is created. The dark-staining epithelial cells which make up the new growth in the cortex of the ovary show occasional mitoses. In many instances the ovary is found to be composed of a medullary portion of lutein cells with partial degeneration and a surrounding cortical layer of tubular, adenomatous, epithelial tissue.

The ultimate picture in this series of changes, if tumor growth does not occur, is represented by Fig. 1D, obtained from a mouse fifteen months after irradiation. The ovary appears shrunken and small. The surface epithelial proliferation which had at first encircled the partially degenerating lutein cells, completely replaces this structure. The final result is that of a small cellular body composed of irregularly distributed, dark-staining, epithelial cells with occasional glandlike formations. No fat is demonstrable in the latter, nor are they accompanied by estrogenic effects.

## DESCRIPTION OF OVARIAN TUMORS

Of those mice that were killed in the period of ten to fifteen months after irradiation, 22 showed the presence of unilateral or bilateral ovarian tumors. The largest of these was 2.5 cm. and the smallest a few millimeters in diameter. Most of the tumors had a yellowish color, and some grayish. Partial degeneration and hemorrhage were occasionally noted grossly. Only those new growths were considered tumors in which the proliferation obviously obliterated the essential architecture of the ovary.

Two main types of tumors were found: a tubular adenoma, originating from the surface epithelium, and parenchymal lutein tumors derived from the ovarian parenchyma. The former have no hormonal implications, while the latter show definite estrogenic effects.

For purposes of simplification, we shall consider the parenchymal tumors in three categories; namely, a granulosa cell type, a thecalike cell type, and a lutein cell type. Actually, none of these is found pure except an occasional completely luteinized form. In 5 cases the granulosa cell dominated the tumor. In only one of the neoplasms did the predominating cell simulate those of the theca interna. Both the granulosa and thecalike tumor cells contain small amounts of doubly refractile fat. The remaining tumors, in which luteinization becomes extreme, are classified as the lutein cell type only on the basis of a quantitative difference in fat content.

*Granulosa Cell Type.*—Mouse 7-8. Killed thirteen months after irradiation. The left ovary was replaced by a spherical, smooth, grayish yellow tumor measuring 2.5 by 2.5 by 2 cm. (Fig. 3). The right ovary was minute, otherwise not unusual.



In short, the evolution and definitive structure of each of the tumors is dependent on a dichotomous growth tendency from a single undifferentiated stem cell—the parenchymal cell of the ovary. The ultimate luteinization varies quantitatively and is superadded.

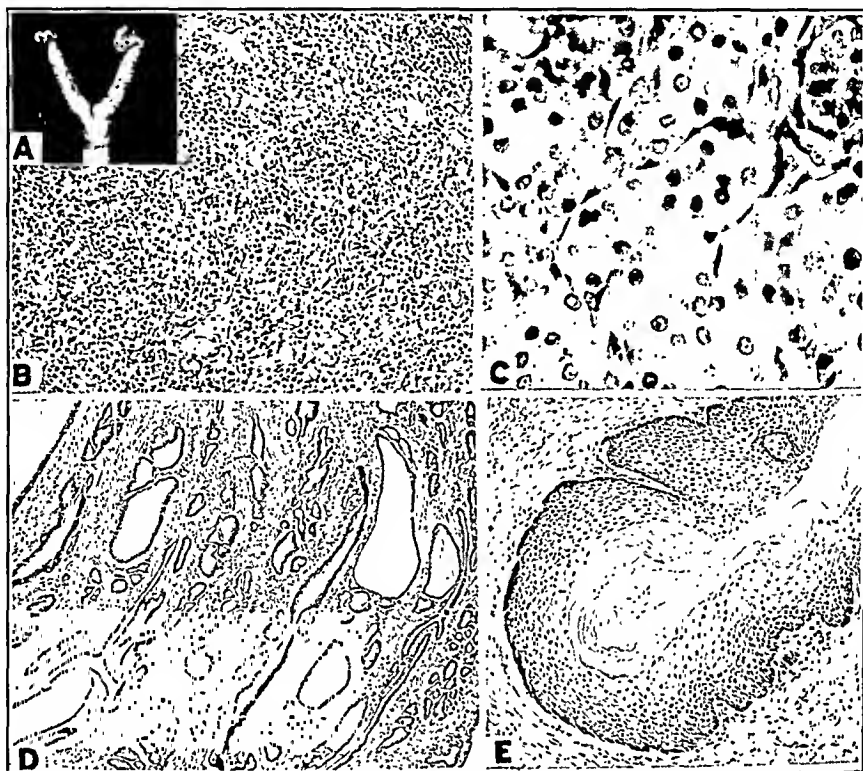


Fig. 5.—Mouse 4-2. Parenchymal tumor of the lutein cell type. *A*, Gross appearance of small tumor in left ovary. Enlargement of uterine horns. *B*, Microscopic appearance of tumor (low power). *C*, Large luteinized cells with foamy cytoplasm containing anisotropic fat. *D*, Cystic hyperplasia of endometrium. *E*, Proliferation of vaginal epithelium with cornification.

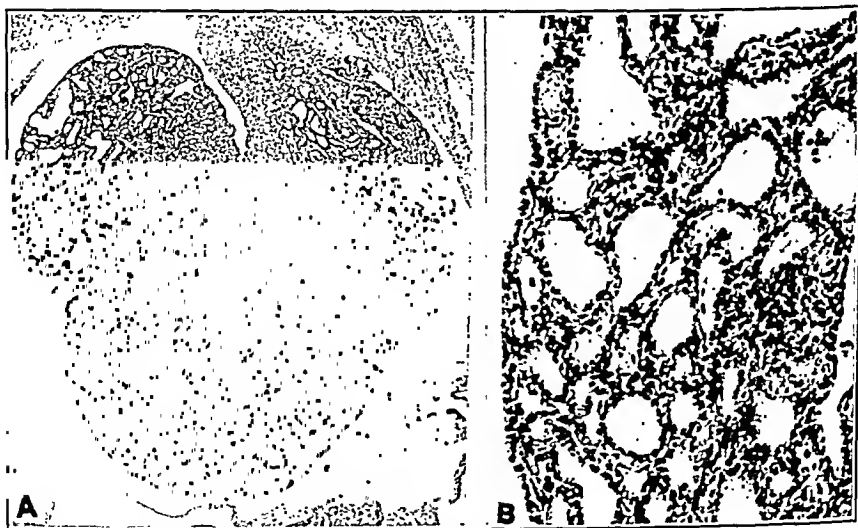


Fig. 6.—Mouse 3-10. *A*, Tubular adenoma arising from proliferation of surface epithelium. *B*, The tubular downgrowths form cystic glandlike structures.

*Thecalike Cell Type.*—Mouse 4-6. Killed fourteen months and nine days after irradiation. The left ovary was the site of a whitish tumor 0.9 cm. in diameter (Fig. 4).

Microscopically, a small crescent of ovarian tissue was found. The tumor was composed of large sheets of cells arranged in streams in the fashion of nonepithelial, rather than epithelial cells. The cells were elongated with large, oval, rather vesicular nuclei and had an ill-defined, slightly vacuolated, eosinophilic cytoplasm. They resembled the cells of the theca interna showing early luteinization. Mitoses were moderate in number. Some portions of the tumor exhibited smaller, rounder cells resembling more the granulosa type. Most of the cells showed some degree of luteinization. The fat they contained was anisotropic. Scattered throughout were typical large foamy lutein cells.

The endometrium showed moderate proliferation.

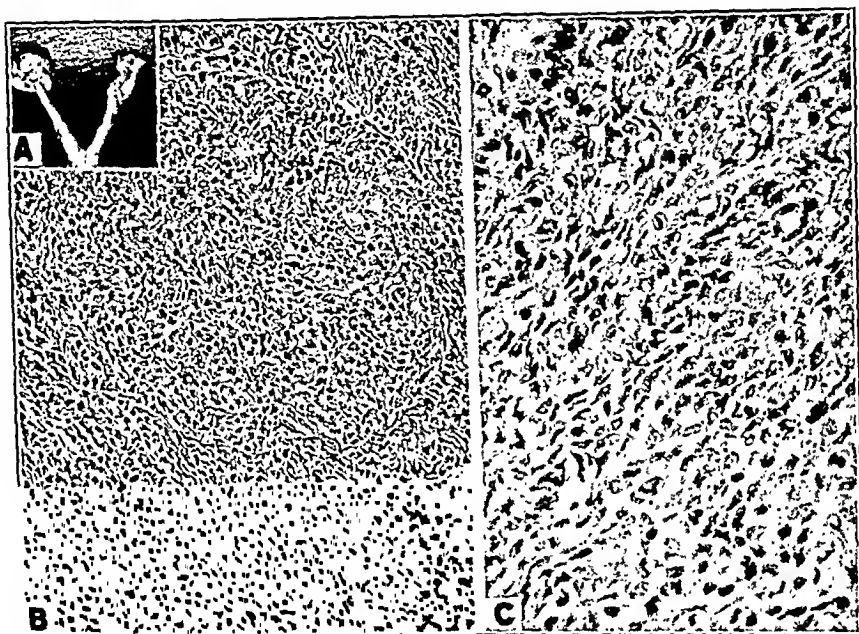


Fig. 4.—Mouse 4-6. Parenchymal lutein tumor of the thecalike cell type. A, Gross appearance of tumor in right ovary. Slight enlargement of uterine horns. B, Microscopic appearance of tumor (low power). C, Same (high power) showing resemblance of cells to those of theca interna.

*Lutein Cell Type.*—Mouse 4-2. Killed sixteen months, eleven days after irradiation. The left ovary contained a round yellow tumor measuring 0.4 by 0.5 cm. (Fig. 5). The right ovary was small. The uterus and uterine horns were thick.

On microscopic examination, the great part of the left ovary was replaced by confluent nests of large luteinized cells having a foamy, eosinophilic cytoplasm. The cortex of the ovary still persisted as a thin shell of small, dark spindle cells compressed against the tunica albuginea. At one pole of the ovary the germinal epithelium had grown down into the tumor in the form of tubules and glandlike structures, the cells of which retained the appearance of the surface epithelium.

The right ovary presented an undifferentiated parenchyma into which there had been an extensive downgrowth of tubular germinal epithelium. In addition there were sporadic, small nests of large, foamy cells.

The endometrium presented an extensive cystic hyperplasia. The vaginal epithelium was markedly thickened, with conspicuous cornification.

It must be stressed again that the tumors just described have been chosen out of the entire group because each represents an extreme development in one direction or another. Actually the granulosa cell and theca cell differentiations proceed side by side within the same tumor. In addition, luteinization becomes superimposed on both lines of cellular differentiation and reaches its highest intensity in the lutein type of tumor.

entire mouse was exposed to the roentgen rays. Regaud and Lacasagne<sup>15</sup> have shown that the hypophysis is resistant to x-rays. Whether or not the hypophysis is actually stimulated by irradiation is a matter of conjecture. Further investigations in this direction are being pursued.

It is concluded that biologically active luteinized tumors produced in the ovaries of irradiated mice are derived from the undifferentiated parenchymal cell of the ovary. The granulosa cells of the Graafian follicle play no role in the genesis of the tumors. The theca interna cells, however, participate with the parenchymal cell in the early post-radiation proliferation and luteinization.

The feminizing neoplasms of the human ovary resemble those produced in mice. They include the granulosa cell tumor and its more luteinized variant—the “*folliculome lipidique*” of Lecène and the theca cell tumor. We do not consider the so-called luteoma a distinct entity. It is our impression that the reported cases of luteoma may fall into one of several categories, namely, granulosa cell tumor with marked luteinization, adrenal rest tumor or metastatic carcinoma.

Robert Meyer<sup>16</sup> suggested that granulosa cell tumors were derived from persisting embryonic “granulosa cell rests” which proliferated in later life under the influence of some unusual stimulus. He based this theory upon the isolated finding in the ovary of a forty-five-year-old woman of small masses of cells resembling those of the granulosa. Similar nests of cells were seen in the ovarian medulla of full-term fetuses and young infants. The great difficulty in finding such embryonic rests in normal ovaries of adult women militates against the “*granulosaballen*” concept of Meyer. Furthermore, we have experienced the ease with which a tangential section of a normal follicle may be mistaken for such “rests.” Robinson’s<sup>21</sup> contention that the tumor arises from mature granulosa cells of the Graafian follicle has not attracted many adherents. The granulosa is a well-differentiated tissue, satellite to the ovum and possibly dependent on it for its existence. Finally, granulosa cell tumors may occur years after the menopause, when follicular activity has long since ceased.

Our studies<sup>12</sup> of a number of theca cell tumors of the ovary reported previously suggest that genetically the theca and granulosa cells have a common origin. This is in accord with Fischel’s concept that it is not the surface epithelium but the premature mesenchyme of the ovary which gives rise to the parenchyma, theca and granulosa cells. Theca cell tumors may show a variegated cell structure including fibromatous tissue, interlacing bundles of plump, epithelioid cells containing doubly refractile fat and rounded, more luteinized cells. These variations are attributable to the same differences in cell differentiation and physiologic response which obtain in the mouse tumors. Tumors containing both theca and granulosa elements have been described.<sup>14</sup> Such tumors merely illustrate a bilateral development from a common stem cell.

A group of cases are now being studied which reveal that in certain endocrinologic disturbances, especially those included in the broad term

*Tubular Adenoma*.—Mouse 3-10. Killed fourteen months, twenty-three days after irradiation. One ovary measures 0.3 by 0.3 cm. (Fig. 6) and the other 0.1 by 0.2 cm. Uterine horns are not enlarged. Vaginal smears over a period of several days before death were of the anestrus type.

In both ovaries tubular and glandlike, downward proliferations of the surface epithelium have almost entirely replaced the ovarian tissue. The cells of these downgrowths are similar to those of the germinal epithelium. Some glands have undergone cystic dilatation. Infrequent mitoses are found. Occasional degenerating luteinized parenchymal cells are noted.

The endometrium shows slight proliferation. The vaginal mucosa is atrophic.

#### HORMONAL ACTIVITY IN PARENCHYMATOUS LUTEIN TUMORS OF MICE

The biologic activity of these neoplasms is expressed by the effect produced upon the uterus and vagina. The quantitative response does not depend upon the size of the tumor or extent of luteinization. The endometrium of the uterus shows distinct evidence of proliferation, often to the extent of cystic hyperplasia. The vaginal mucosa in several instances show a full proliferative effect, with thickened epithelium and cornification. Others present surface mucification. Only occasionally is a full estrus vaginal smear obtained. Several attempts were made to transplant portions of the granulosa cell type of tumor into the axillae of castrated mice. Vaginal smears in the host mice taken daily over a period of ten days all proved negative.

Histologic examination of the transplants showed degeneration of the tumor cells. The degenerated tumor cells have a striking resemblance to the excessively foamy, large lutein cells.

#### DISCUSSION

Although the biologically active tumors produced in mice after irradiation present variations in cellular differentiation and intensity of luteinization, their origin appears identical. The determination of the source of these neoplasms is dependent upon the interpretation of the earliest changes noted after irradiation. Our studies have led us to conclusions which in some respects differ from those of other authors. We believe that the granulosa cells within the follicles do not persist long after irradiation and do not proliferate to give rise to tumors. They appear to degenerate in the wake of ovum destruction. With the elimination of these structures there remains only interfollicular parenchyma together with persisting and proliferating theca interna cells. The term parenchyma is applied to the interfollicular tissue to indicate its functional potencies. The first evidence of growth is signaled by the simultaneous proliferation and luteinization of the theca interna and parenchymal cells. Thus a hyperplastic substrate or groundwork is established upon which neoplasia may appear many months later. So far as we have been able to determine, proliferation and luteinization progress together. We did not observe a primary proliferation and secondary luteinization of the newly formed cells.

It is generally accepted that luteinization is an effect of stimulation from the anterior lobe of the hypophysis. It must be recalled that the

# A STUDY OF THE RETICULUM AND OF LUTEINIZATION IN GRANULOSA AND THECA CELL TUMORS OF THE OVARY\*

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GRANULOSA cell tumors, which were first described by von Kahl den in 1895, now occupy a well-established place in the pathology of the ovary. The folliculomatous, cylindromatous and undifferentiated variations of the granulosa tumor are generally well recognized. However, the lipoid changes or so-called luteinization which any form of the tumor may undergo are not so well known or so well understood, not only because they are much less frequently seen, but also because they have not been so intensively studied.

Our interest in the process of luteinization in these tumors arose, in part, because we encountered a large, nearly completely luteinized human tumor, but more particularly because in a previously reported study of granulosa cell tumors which were artificially produced in the ovary of the mouse by means of x-ray radiation, the luteinized tumors were found to be very common. In a series of 52 mouse tumors, luteinized forms were encountered with such frequency (42 per cent) that it was possible to study the different stages of the process in detail. Inasmuch as human luteinized tumors are difficult to obtain, the mouse tumors furnish a material which permits the filling of gaps that otherwise would remain open. The purpose of this report is to convey some of the information that has accumulated to date.

At the outset it may be well to state that so-called luteinization of the human granulosa cell neoplasms is not so uncommon as many have thought. This conclusion is based upon a careful survey of the entire literature upon the subject of granulosa tumors, as well as that of "luteomas" and those tumors of the ovary which have been classified as hypernephromas. Of completely luteinized human tumors, or so-called "luteomas," 9 instances have been found which may be accepted with little or no question (Table I). Seventeen granulosa tumors have been reported showing lutein changes to a major degree (Table II). Minor luteinization is of comparative frequency, consequently no attempt is made toward a complete survey. A considerable number of tumors, which have been reported as luteomas, cannot be accepted as properly belonging to this category either because they can be identified as belonging to some other group or because insufficient data are available to classify them definitely.

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of ovarian-adrenal syndrome, the human ovary may show proliferation and partial differentiation of the parenchyma with patchy luteinization.

#### SUMMARY

X-ray irradiation of mice at puberty results in the production of two types of ovarian tumors: tubular adenomas derived from the surface epithelium and parenchymal lutein tumors.

The parenchymal lutein tumors alone exhibit hormonal activity expressed in proliferative changes in the endometrium and vaginal mucosa.

Histologically, these tumors are composed of granulosa and theca cells with varying degrees of luteinization. They are entirely comparable to the granulosa cell tumor and its excessively luteinized variant, the Lecène tumor, and the theca cell tumor of the human ovary.

The luteinized ovarian tumors in mice are derived from the undifferentiated parenchyma. While the theca interna cells participate in the early proliferation and luteinization, the mature granulosa cells play no role in the genesis of these neoplasms.

The histogenesis of the analogous human tumors may well be identical.

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the one hand, and the lipid content of the lutein cells of the sow's ovary, on the other, is most significant (Figs. 1 and 2). These workers conclude that the phospholipid content of the lutein cell as demonstrated by histochemical tests is an index to its potential activity, and the ratio of phospholipid to cholesterol is an indication of actual or resultant activity emanating from metabolism within the cell. The fact that these values vary directly with the output of hormones (Table V) is most significant, particularly when it is remembered that estrone and progesterone are sterol derivatives.

Inasmuch as the term luteinization has come to mean such specific and definite changes in the normal granulosa cell, it may be instructive to examine the neoplastic cells of similar origin to determine whether

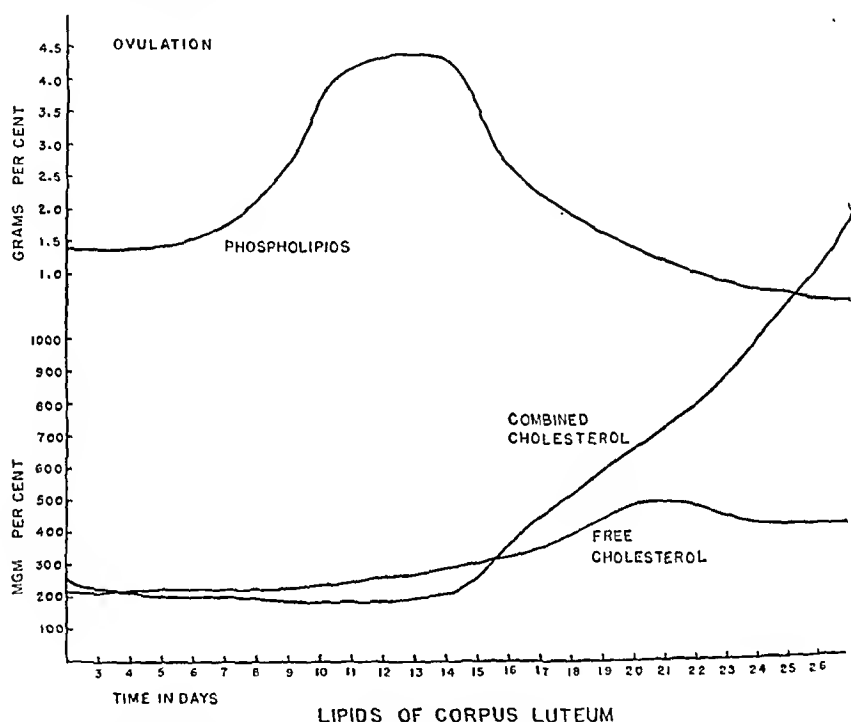


Fig. 1.—Graph showing the concentration of phospholipids, combined cholesterol, and free cholesterol in the corpus luteum of the sow's ovary in the various days after ovulation. (Bloor, Okey and Corner.)

TABLE III. CYTOLOGIC CRITERIA OF LUTEINIZATION AND FATTY DEGENERATION OF THECA AND GRANULOSA CELLS

		LUTEINIZATION	FATTY DEGENERATION
Macroscopic:	Yellow (Carotin) Pigmentation	Marked	Slight or absent
Microscopic	Hypertrophy Golgi body	15 to 45 Micra	Irregular
	Mitochondria	Enlargement and fragmentation	Displaced to one pole or absent
	Nucleus	Shortening and disappearance of rods	None present
Chemical	Lipoids	Normal	Various stages of chromolysis
		1. Phospholipids 2. Free cholesterol 3. Combined cholesterol	1. Neutral and acid fats 2. Esters 3. Soaps

TABLE I. LUTEOMAS

1908	Gardner and McCleary
1913	Massabuau
1918	Gordon } Accepted upon Turnbull and Leith
1920	Gordon } Murray's careful analysis
1927	Wolfe, S. A.
1931	Cosacesco, Draganesco, Georgesco, Dinischiotu
1931	Habbe, K., Case 18
1937	Torres, P. R.
1938	Viana, O.

TABLE II. GRANULOSA TUMORS LUTEINIZED TO A MAJOR DEGREE

1899	Gottschalk, S.
1902	Michelazzi
1910	Christian, E.
1922	Aschner, B.
1927	Lecène
1928	Cattaneo, L.
1933	Plate, W. P.
1934	Benda and Kraus
1934	Novak, E.
1935	Cutler, O. L.
1935	Decoulx, BéDrine and Bastien
1935	Wills and Romano
1936	Vayssiere, Mosinger, etc.
1937	Bourg & Roemans
1938	Delarue and Isidor
1938	Thomson and Stabler
1939	Traut, Kuder and Cadden

It is interesting to note that during the twenty-eight years following the report of the first luteinized tumor by Gottschalk in 1899, only 5 tumors showing lutein changes were reported; whereas, since Lecène again brought this type of tumor to the attention of the profession in 1927, 12 examples have been noted, and of these, 10 have appeared in the past six years. This would seem to promise more frequent mention and greater familiarity with this type of tumor in the future.

What is the nature of the metamorphosis which the granulosa cell undergoes in its transformation into a lutein cell? We know that in the normal Graafian follicle there are marked changes in the granulosa cells which may be specifically described as: (1) an increase in size of the cell from 15  $\mu$  to about 45  $\mu$  in diameter; (2) an alteration of the mitochondria from long rods (Levi) or intricate networks (Chydenius) to short fragments which finally disappear (Horrenberger); (3) an enlargement of the Golgi network, which is followed by a process of involution, in which the net assumes a position more remote from the nucleus (Riquier); (4) whereas mitoses are frequent in granulosa cells, they are seldom observed in lutein cells; (5) and finally, there is a marked change in the lipoid constituents, such that during the phase of hormonal activity of the cell there is an increase in phospholipid and cholesterol content, both of which are subsequently replaced by cholesterol esters and fats (Table III).

The work of Bloor, Okey and Corner, as well as that of Boyd and Elden, correlating the relationships between physiologic activity, on



those mice which had survived longest after the radiation of the body (Fig. 3). This has suggested the possibility that lutein changes may be a function of the maturity of the cell rather than a response to hormonal influence from the anterior hypophysis, as is indicated by the currently accepted concept of the cause of luteinization. In addition to this observation, one of the mice had bilateral ovarian tumors,

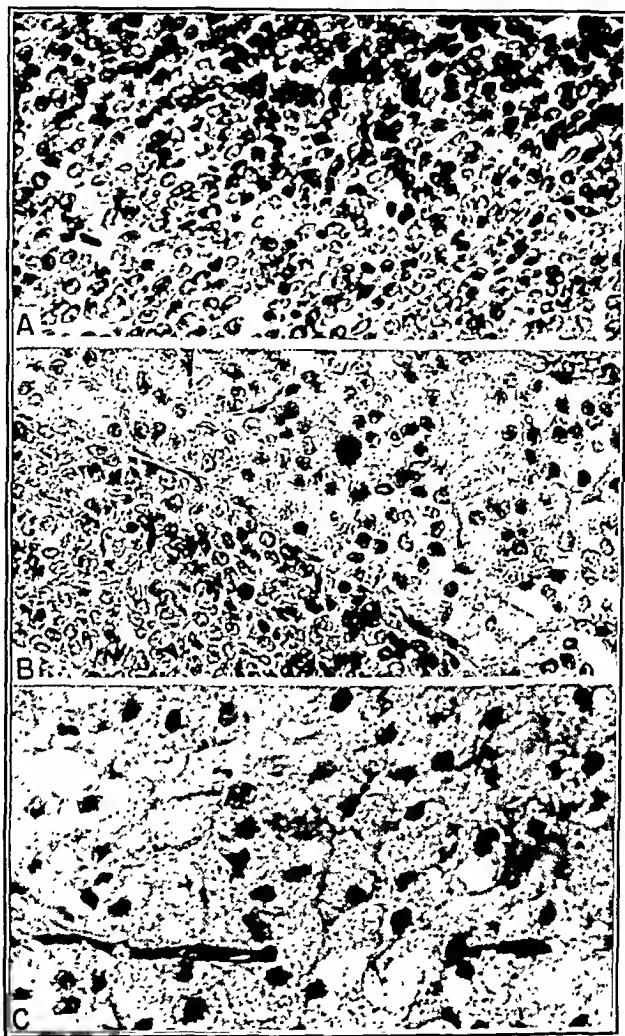


Fig. 4, A, B, C.—Hematoxylin and eosin stain. Zenker-formol fixation. ( $\times 520$ .) A, A section from the granulosa tumor of the mouse's ovary, showing little or no differentiation and no attempt at luteinization. B, A section from the granulosa cell tumor of the mouse's ovary undergoing a process of luteinization. C, A section from the granulosa tumor of the mouse's ovary, showing almost complete luteinization.

one of which was completely "luteinized," while the other was distinctly granulosal in character. The possible role of maturity in the production of the so-called luteinization of the granulosa tumors also suggests strongly that the accumulation of fat may be primarily a matter of senescence or degeneration, and therefore not strictly analogous to luteinization as we understand it in the normal Graafian follicle (Fig. 4, A, B, C).

or not the same or similar changes take place, and to differentiate between luteinization, on the one hand, and fatty degeneration, on the other.

Early in our study of the mouse tumors it was noted that, with few exceptions, lutein changes occurred in the older neoplasms, that is, in

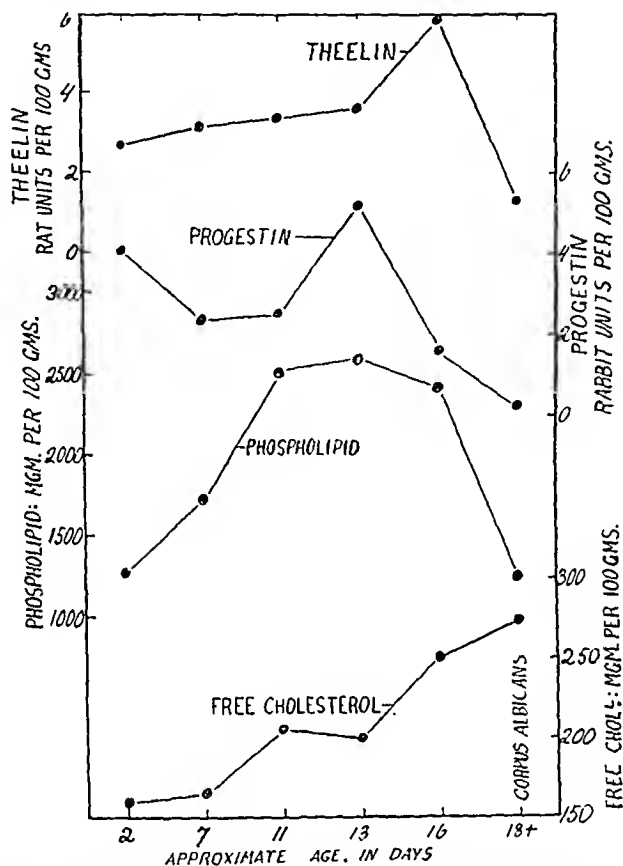


Fig. 2.—Graph showing the relationship of phospholipids and free cholesterol to the theelin and progestin in the corpus luteum of the sow's ovary in the various days after ovulation. (Boyd and Elden.)

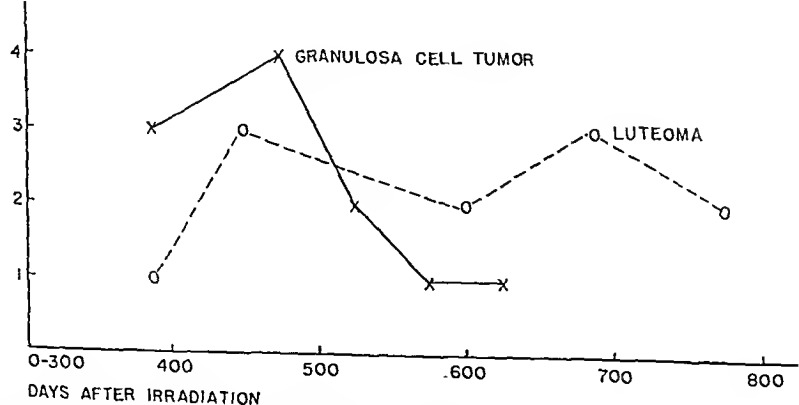


Fig. 3.—Showing the age incidence of granulosa cell tumors in the mouse's ovary as compared to the incidence of lutein tumors. It would seem that in general the lutein tumors are definitely of greater age than are the granulosa tumors.

ing reactions of the cells in the evaluations of their biologic activity. For similar reasons we have not been able to study the more minute details of cellular architecture, such as mitochondria and Golgi networks, for they rapidly disintegrate with ordinary fixation; therefore, evaluation of these must be reserved for a later report.

In recent years, the use of stains in their application to the study of reticulum and of lipid substances has been greatly advanced. To

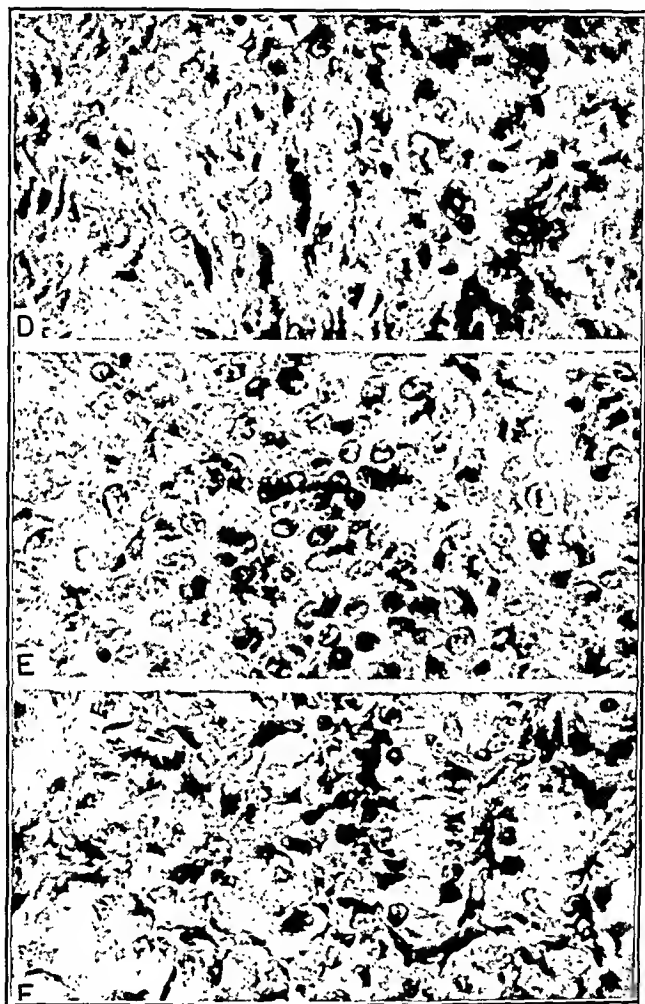


Fig. 5, *D*, *E*, *F*.—Human granulosa cell tumors. Zenker-formol fixation. ( $\times 520$ .) *D*, A section from Tumor 4 of the theca-granulosa type, showing a portion of the tumor which is predominantly thecal in character. *E*, Another portion of Tumor 4, showing granulosa cells predominating, with commencing luteinization. *F*, A section from Tumor 5, which is a granulosa cell tumor that is almost completely luteinized, showing characteristic lutein cells.

demonstrate the reticulum, we have used the Foot silver stain. In the visualization of lipid and fatty substances, the osmic acid-Sudan technique of Hoerr and Romeis has made possible the histologic demonstration of the intracellular lipid and lipid content. To the latter we shall return, but first let us consider the reticulum (Fig. 6, *A*, *B*, *C*, *D*, *E*).

Since we are interested primarily in gaining knowledge which may be of value to the human patient, most emphasis has been placed upon the study of the human tumors, using the mouse tumors only as a source material to which we could refer for corroborative or negative evidence. This communication is based on a study of five human tumors, one of which shows marked luteinization, the second lutein changes to a lesser degree, while two are typical, well-differentiated

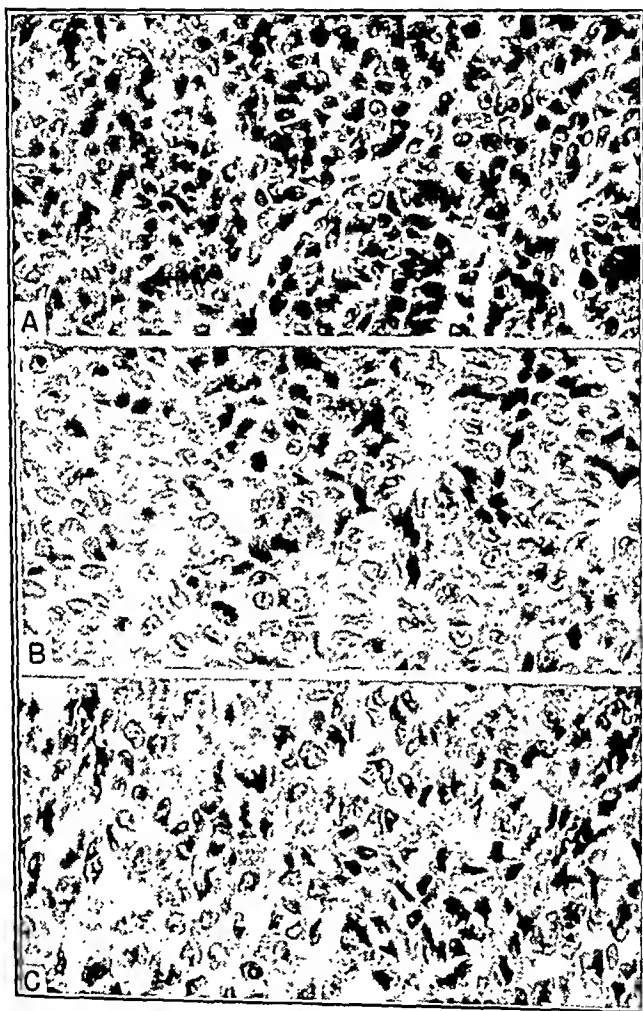


Fig. 5. A, B, C.—Human granulosa cell tumors. Zenker-formol fixation. ( $\times 520$ .) A, A section from Tumor 1, showing a portion of the cylindromatous type of tumor, with very little differentiation. B, A section from Tumor 2 showing the Call and Exner bodies and an occasional lutein cell. C, A section from Tumor 3 showing beginning lutein changes.

granulosa tumors, and the fifth is a tumor which may be characterized as being borderline between the granulosa and theca cell varieties (Fig. 5, A, B, C, D, E, F).

Because our material had been fixed in formalin, hormone assay could not be carried out, and we were therefore dependent upon (1) the endometrial response; (2) the chemical analysis; and (3) the stain-

line of demarcation between the theca and granulosa cells when the silver stain is used is so sharply drawn that it is impossible to confuse the two types of cells. In the mature corpus luteum, the same relationship maintains to a lesser degree (Fig. 6, *B*) in that the theca lutein cells are always surrounded by reticulum, the strands of which grow more and more dense, whereas the granulosa lutein cells are involved in a gradually increasing network of the finest terminal strands.

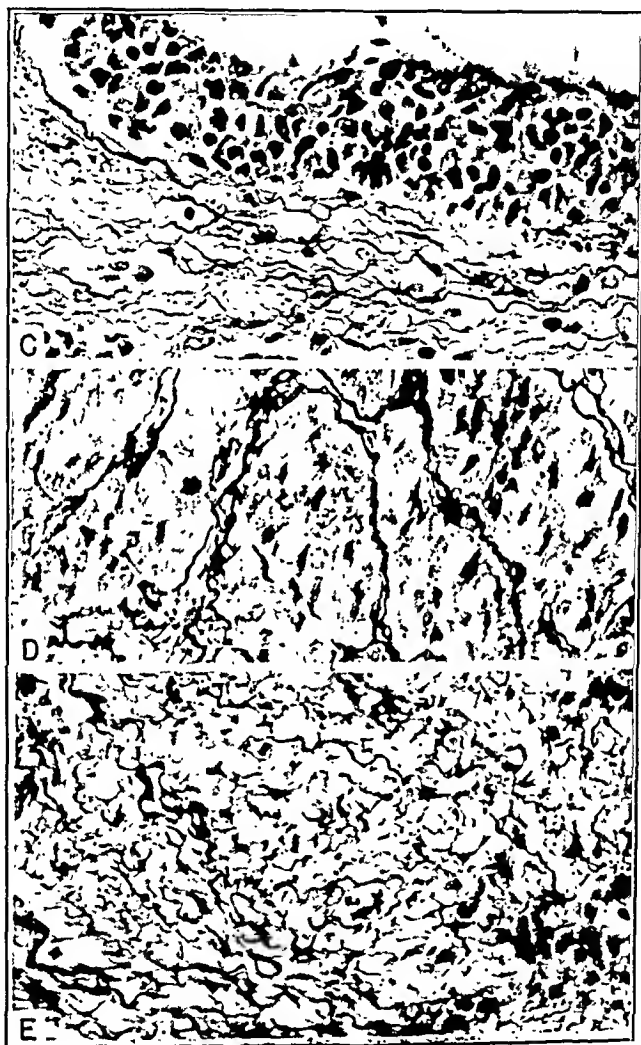


Fig. 6, *C, D, E*.—Stained with Foot's silver stain. ( $\times 520$ .) *C*, A section from the folliculomatous type of granulosa cell tumor. The granulosa cell layer is very distinct and separated from the lamina propria composed of reticulum in which are enmeshed theca-lutein cells. *D*, A section from a luteinized granulosa cell tumor showing islands of lutein cells separated by fine network of reticulum. Individual lutein cells are quite free of any reticular involvement. *E*, A section from the theca-granulosa cell tumor showing the theca cells enmeshed individually and a very extensive reticular framework.

However, the granulosa lutein cells are never so completely enmeshed as is the case with the theca cells.

This relationship of reticulum to the two types of cells is very helpful in studying tumors of theca and granulosa origin, for one can

Since Loeffler and Priesel first described the theca cell neoplasms, pathologists have striven to decide whether the tumor should be considered as a separate entity or simply another variety of granulosa cell tumor. Recently there has been an increasing tendency to consider them as very closely related, some observers going so far as to say that the theca cell tumors cannot be established as a separate group



Fig. 6, A, B.—Stained with Foot's silver stain. ( $\times 520$ .) A. A section from the margin of the normal, recently ruptured Graafian follicle, showing the granulosa layer, distinctly demarcated from the theca by the reticulum. Each thecal cell is distinctly surrounded by the net of reticulum. B. A section from the normal corpus luteum, showing the relationship of the reticulum to the theca-lutein and granulosa lutein cell. The lower margin shows a few of the theca-lutein cells enmeshed in dense reticular structures. The middle portion shows the granulosa lutein cells with only slight filaments of reticulum penetrating this layer.

of tumors, basing their opinion upon the discovery of tumors made up of both elements. This study, with the use of the silver stain, tends to strengthen the latter view.

By referring to Fig. 6, A, representing an early stage in the development of the corpus luteum, the intimate relationship of the reticular envelope to each individual theca cell is clearly shown. In fact, the

By this treatment the phospholipid substances stain a faint rose pink, the free cholesterol takes a yellow amber color, and the esters, neutral and acid fats stain black (Fig. 7, *A, B, C, D, E*).

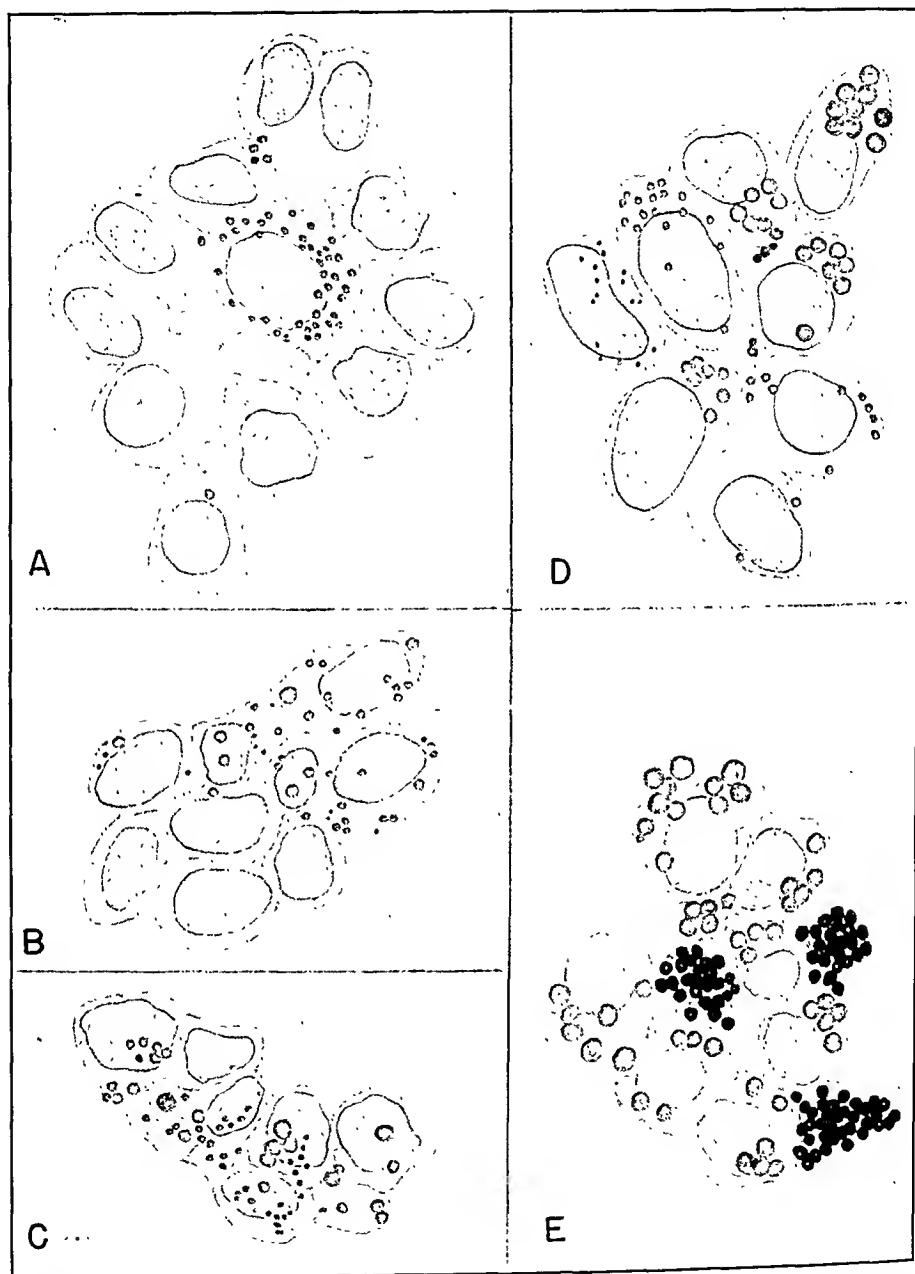


Fig. 7.—Camera-lucida drawings of representative sections from each of the five human tumors included in this study, stained by the Hoerr-Romeis technique to demonstrate phospholipids, fats and esters. *A*, A section from Tumor 1, showing small quantities of phospholipids (pale staining), in minute droplets. *B*, A section from Tumor 2, showing a greater concentration of phospholipid droplets which are indicated in the very pale gray as well as darker staining, cholesterol or cholesterol esters. *C*, A section from Tumor 3, showing some phospholipid (pale), with considerable representation of cholesterol droplets (dark), and some very dark-staining osmic reaction (black). *D*, A section from the theca-granulosa tumor, showing very considerable droplets of phospholipids, cholesterol and the more saturated fats and fatty acids. *E*, From the luteinized granulosa cell tumor, showing almost no phospholipids, a moderate amount of cholesterol, large quantities of cholesterol esters, fatty acids, neutral fats, and so forth.

thereby differentiate between the two types of cells with a very satisfactory degree of certainty (Fig. 6, *C*, *D*, *E*).

Furthermore, the use of this criterion convinces one that in the well-differentiated or folliculomatous types of granulosa cell tumors, as well as in the more undifferentiated types, we actually have representatives of both cellular layers of the Graafian follicle. In other words, many so-called granulosa cell tumors contain considerable quantities of thecal elements. It seems probable that further study will reveal that we should not draw too close a line of demarcation between theca cell tumors, on the one hand, and granulosa cell tumors, on the other. Their physiologic activities are identical, and as we know more about their cytologic relationships, it seems more than likely that we shall conclude that every tumor of this general category contains elements composed of representatives of the two varieties of cell. We have come to the conclusion, tentatively, that this is true, basing our opinion upon the human material thus far examined. However, a more exhaustive study must be made upon many tumors before a definitive conclusion can be reached. This work is already under way in our laboratory upon 50 granulosa tumors collected from a number of hospitals in New York City.

We turn now to a consideration of the lipid and fatty changes as found in the human tumors. As a result of the chemical studies of Bloor, Okey and Corner, as well as those of Boyd and Elden, we may assume that in the sow's ovary, at least, the percentage content of phospholipid varies markedly with the activity of the gland, and in direct proportion to its hormonal output. These workers have shown that the phospholipid content of the cells is from two to three times as high during pre-estrus and pregnancy as during periods of development or regression of the gland. Free cholesterol also increases up to and including the same periods, but to a much smaller degree. On the other hand, cholesterol esters vary inversely with the activity of the organ. Therefore, we may say that a high phospholipid content of lutein tissue is a characteristic of physiologic activity. If this concept is correct, it is possible to measure the physiologic activity of a tissue without resort to a direct analysis of the hormonal output. Such an analysis may be done by determining the phospholipid, free cholesterol, and the cholesterol ester content in the chemical laboratory. Another means of evaluating the lipid potentialities of a tissue is by use of the Hoerr-Romeis lipid staining technique (Table IV). This procedure has the advantage over chemical analysis of enabling one to see just what cells or what portions of the tissue are active, inactive, or degenerate.

TABLE IV. HOERR-ROMEIS TECHNIQUE FOR STAINING LIPINS

1. Fixation in Zenker-formol solution, 24 hours
2. Mordant in 3 per cent potassium dichromate solution, 2 days
3. 2 per cent osmic acid, 6 days
4. Embedding in gelatin
5. Frozen sectioning
6. Stain with Romeis' sudan III solution, 12 to 16 hours



From the data presented, the Sudan III reaction indicating the presence of phospholipids in the cells may be said to parallel the phospholipid content of the tumors as determined by chemical analysis. The same statement is true of the end-products of lipid metabolism, that is, the content of neutral fats, fatty acids, and esters is correspondingly indicated by the osmic acid reaction.

From a comparative study of these hormonally active tumors, using the chemical evaluation of the lipid content as one factor and the response to fat stains as another, certain conclusions can be drawn. It is at once apparent that, with the exception of Case 2, the phospholipid content of these tumors is small as compared with that of the normal corpus luteum, where values range from 800 to 2,700 mg. per cent. On the other hand, the free cholesterol values are much higher than in the normal corpus luteum. A completely satisfactory explanation of the significance of the low phospholipid-cholesterol ratio is not apparent, however; in spite of the low ratio, the tumors achieve an endometrial reaction which is more marked in its extent than is seen as a result of normal Graafian follicle effect which must be accounted for by the greater cell mass of the tumors and the fact that they produce their hormonal influence over much longer periods of time.

It also seems obvious that in a general way the phospholipid and free cholesterol content is somewhat parallel to hormonal activity, although hormone assays will need to be done on a similar group of tumors before this conclusion can be accepted without reservation.

In contrast to the corpus luteum, where most of the cells develop at about the same rate, and there is only moderate difference in the degree of maturity, in the granulosa tumor undergoing lipid change there are the widest variations between foci of recent growth and others of marked maturity and even senescence. Parts of such a tumor, therefore, show a predominance of the phospholipid phase of metabolism, whereas others are rich in neutral and acid fats. The first, or phospholipid phase, is characteristic of hormonal potentialities and the latter, impotent, representing the end stages of the process of lipid metabolism. The tumor, therefore, is composed of many areas with varying degrees of biologic activity and the effect of the neoplasm upon the body is a composite of the whole. This concept indicates clearly the greater difficulties and complexities encountered in the study of the neoplasm as compared with those attending an evaluation of the normal tissues.

It would seem, as far as one may judge at the present time, that the granulosa cell tumors may be said to undergo luteinization much as do the normal cells of the Graafian follicle in the sense that the lipid metabolism of both is similar. Whether the transformations of mitochondria and the Golgi bodies, which are thought to be the chief repositories of the lipid elements, are analogous remains for further study to determine.

The granulosa cell neoplasm, similar to tumors in general and in contrast to the ovarian follicle or corpus luteum, is subject to accidental complications of its vascular supply by virtue of the fact that

Using the chemical and histologic methods of study upon the 5 human tumors, we find the following relationships existing between the lipid content and the staining reactions, as compared to the clinical evidence of hormonal activity (Table V).

CASE 1.—A typical granulosa cell tumor of the cylindromatous type, measuring 15 by 8 by 7 cm., produced a marked hyperplasia of the endometrium in a woman three years beyond the menopause.

It contained 350\* mg. per cent phospholipid, 580 mg. per cent free cholesterol, and 990 mg. per cent total cholesterol. The total fat content was 1070 mg. per cent. The fat stain reactions were sudan ++++ and osmic acid +.

TABLE V. SHOWING THE CONSOLIDATED RESULTS OF THE STUDY OF FIVE HUMAN TUMORS

TYPE OF TUMOR	ENDOMETRIAL HYPERPLASIA	SUDAN III REACTION	OSMIC ACID REACTION	PHOSPHOLIPID MG. %	FREE CHOLESTEROL MG. %	TOTAL CHOLESTEROL MG. %	TOTAL FAT MG. %
1. Granulosa	++++	++++	+	350	580	990	1,070
2. Granulosa	++++	++++	+	1,620	830	800	1,870
3. Granulosa	++	++	+++	310	890	1,120	3,775
4. Theca							
granulosa	++++	+++	++	520	370	710	2,822
5. Luteinized granulosa		+	++++	170	880	1,230	4,130

CASE 2.—A folliculomatous type of granulosa cell tumor measuring 2 by 3 by 5 cm., which also produced a marked hyperplasia of the endometrium in a woman of 40 years, who had had excessive metrorrhagia at four-month intervals for two and a half years.

This tumor contained 1,620 mg. per cent phospholipid, 830 mg. per cent free cholesterol, and 800 mg. per cent total cholesterol. The total fat content was 1,870 mg. per cent. The fat stains showed sudan ++++ and osmic acid +.

CASE 3.—A well-differentiated cylindromatous granulosa cell tumor, measuring 14 by 15 by 8 cm., produced a moderate hyperplasia of the endometrium in a 43-year-old woman who had had amenorrhea for a period of eighteen months, followed by excessive uterine bleeding.

The chemical analysis gave the lipid relationships as phospholipid 310 mg. per cent, free cholesterol 890 mg. per cent, and total cholesterol 1,120 mg. per cent. The total fat content was 3,775 mg. per cent. The fat stains showed sudan ++ and osmic acid +++.

CASE 4.—A solid, theca granulosa cell type of tumor, measuring 8 by 7 by 4½ cm., producing a marked hyperplasia of the endometrium. The patient was 29 years of age and had experienced amenorrhea for three months, followed by scanty but continuous uterine bleeding.

Chemical analysis showed phospholipids 520 mg. per cent, free cholesterol 370 mg. per cent, and total cholesterol 710 mg. per cent. Total fat content was 2822 mg. per cent. The Hoerr-Romeis stain indicated sudan +++ and osmic reaction ++.

CASE 5.—A very marked luteinized granulosa cell tumor of cylindromatous type, measuring 21 by 17 by 11 cm., and could not be evaluated as to its hormone output because the uterus had been removed eighteen years previously.

The chemical analysis showed phospholipid content 170 mg. per cent, free cholesterol 880 mg. per cent, and total cholesterol 1,230 mg. per cent. The total fat content was 4,130 mg. per cent. The Hoerr-Romeis stain showed only sudan + reaction, while the osmic acid reaction was ++++.

\*All weights are based on dry weight of tumor.

collagenous degeneration followed by fibrosis. In tumors composed chiefly of theca elements, collagenous degeneration and fibrosis are the usual sequelae to the luteinization phase.

Dr. J. Furth of the Department of Pathology, Cornell Medical College, has been most kind in permitting the use of many mouse tumors, as well as in giving friendly advice and criticism, for all of which our thanks are warmly given.

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it is a tumor. In rapidly growing portions of the tumor, the blood supply sometimes becomes inadequate. Such a state is followed by the ischemic necrosis and cyst formation, which are very common findings in most granulosa tumors of good size. Such an accident must inevitably be associated with marked fluctuation in the hormone output by the tumor mass.

These factors in the life history of the granulosa cells elucidate why some granulosa cell tumors are relatively asymptomatic, from the clinical point of view. It also explains why many of the so-called luteomas have shown little or nothing in the way of hormonal activity at the time of observation. For example, amenorrhea associated with granulosa cell tumors is of two kinds, first, that which occurs during the period of active growth of many cells, producing a high titer of estrone and hence, hyperplasia of the endometrium; and second, that due to luteinization of the tumor. Metrorrhagia, on the other hand, is probably present only when there is a drop in estrone titer which presumably follows maturation of the granulosa cells or ischemic necrosis of portions of the tumor.

#### SUMMARY

1. In the Graafian follicle and corpus luteum, as well as in tumors containing theca and granulosa cells, the relationship of the reticulum furnishes a means of identifying the two types of cells. The theca cells are always individually surrounded by this connective tissue element, whereas granulosa cells and lutein cells are enclosed not at all, or as groups of cells.

2. Granulosa and theca cell tumors are not only closely related, but in all probability, most human granulosa cell tumors contain varying proportions of both types of cells.

3. These tumors undergo luteinization in the same manner as does the Graafian follicle. The cause of luteinization is not known, excepting that it is found in the older tumors of the mouse's ovary and may be therefore an expression of age or maturity.

4. The phospholipid content of the tumors is low per unit of weight, as compared with that of the corpus luteum. This may, in part, be due to the greater connective tissue content and areas of degeneration.

5. The life cycle of the granulosa cells, together with the fact that the tumor composed of them contains foci which differ widely in degrees of maturity, explains some of the clinical phenomena observed in patients harboring this type of growth.

6. Luteinization of granulosa cell tumors in small or moderate degree is common. Seventeen instances reported in the literature have been found where the major portion of the tumor had undergone lipid change. Complete luteinization is rare and is usually found in small tumors.

7. If allowed to mature, one of three different terminations is thought to be the end of the life cycle of granulosa cell tumors: (a) luteinization followed by lipid degeneration; (b) ischemic necrosis; and (c)

integration of the follicular apparatus occurs but estrus continues, due to the fact that sufficient estrogenic hormone is elaborated by the parenchymatous cell changes to support this function. We know of course that there occurs a marked decrease in the estrogenic output in castrates. Nevertheless is it not possible that in women treated much less than would be normal, let us say for a carcinoma, but sufficient to cause complete and permanent cessation of menstruation, a change occurs similar to that described for the laboratory animal? I should like to know whether either of the essayists has had the opportunity of studying human ovarian tissue from women who have been subjected to *average* castration doses of x-ray.

DR. GEORGE W. CORNER, ROCHESTER, N. Y.—Is it not possible that the origin of the new cells of the granulosa type is from surviving undifferentiated cortical tissue? It has been noted in experiments on sex reversal in salamanders, that when the male gonad is changed into an ovary, the newly-differentiated cells of ovarian character come from the undifferentiated cortex of the original gonad.

I should like to ask Geist whether he has evidence of the production of corpus luteum hormone by the cells which he described by the word "luteinized"; such evidence would be, for example, a progestational reaction of the endometrium or a mucification of the vaginal epithelium, indicating an interaction of progesterone with estrogen.

DR. GEIST (closing).—In answer to a question that Miller raised, we are not in a position at the moment to report on the status of postradiation ovaries in the human female. However, we have evidence to show that in a large group of cases the estrous phenomena may persist for as long as nine months, as indicated by a normal estrogen excretion and a positive vaginal smear. We know, however, that the follicular apparatus of the ovary is destroyed, but there is still parenchymal tissue which may produce this substance and maintain estrus for three to nine months. We do know that if such rayed ovaries are removed, estrus promptly ceases. This strongly suggests that the rayed ovaries produced sufficient estrogen to cause the estrous phenomena.

Corner raised a question about the surface epithelium in the mice. Parks, in his interpretation of the early radiation changes, thought that in radiated immature mice these parenchymatous changes might be due to surface invasion. In the mature x-rayed mice he found no such invasion. We believe that the surface epithelium in the human being takes no part in the formation of the parenchyma of the ovary. It is formed by a transition in situ of the original mesenchyme, so that theoretically we believe, since the study of the rayed mouse ovary, that the surface of the ovary would be in no way concerned with parenchymal changes that we expect sometimes to find in the human being.

DR. TRAUT (closing).—I have been asked for a word as to how the ovarian tumors are produced in the mouse. In our series they were rayed before the first estrus had taken place and were given about 400 units over the whole body, including the hypophysis. At varying periods of time, usually not less than 300 or 400 days, we began to get adenomatous changes in the ovary which might be called tumor formation. The granulosa cell formation came at a late period, usually 800 to 1,000 days after radiation.

The fact that the radiation in mice produces tumors and the fact that x-ray may stimulate certain cells in the ovary to proliferate, may have some importance in the human being. We have seen several suggestive instances since Butterworth and I gave our paper two years ago. We have had called to our attention four patients who had been castrated by deep x-ray therapy and then subsequently had developed granulosa cell tumor. However, we shall have to have a great deal more experience before we can draw conclusions as to the importance of x-ray therapy as a causal factor in producing granulosa tumors in the human being.

In answer to one of Corner's questions, many of the tumors do produce progesterone. With certain of the mouse tumors we have observed definite secretory phases occurring in the endometrium after it has undergone hypertrophy. In addition the secretory phase of the endometrium has been reported as occurring with luteinized tumors in the human being, notably those of Novak and Johnston and Stabler.

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# DISCUSSION ON PAPERS BY DRS. GEIST, GAINES AND POLLACK, AND TRAUT, KUDER AND CADDEN

DR. NORMAN F. MILLER, ANN ARBOR, MICH.—These contributions have been of great value in clearing away much of the haze which has surrounded the origin, life cycle, and the variable histologic picture of the granulosa cell group of tumors. These studies explain also the inconsistent clinical syndrome associated with such tumors in the human being. Finally on the basis of work here presented I am willing to accept a single stem or cellular precursor. Whether this be embryonic granulosa cell rests, as has been suggested by Meyer, or undifferentiated parenchymal cells as stressed by Geist, requires further study before a decision can be reached. There appears to be little doubt, however, that the granulosa cells of the Graafian follicles play no etiologic role.

By placing the granulosa, theca and so-called lutein tumors in a single group, a real step toward simplification in classification has been made. Since luteinization is merely a phase in the life cycle of these tumors and since both theca and granulosa cellular elements are found in varying proportions, the question of simplified nomenclature might be considered. Why not rename this group of tumors, simply yet significantly?

Since reading these papers I have toyed with the thought that here we may have a clue to the interesting behavior of 30 per cent of women under 40 years of age, castrated by means of radiation. In a follow-up study of approximately 360 noncancerous women between the ages of 35 and 50 treated by means of radiation, Kretzchmar and Brown in my clinic discovered that the so-called radiation menopause has been overemphasized. Thirty per cent of the women under 40 years of age, when treated with what was considered to be an adequate castration dose of either x-ray or radium, and in whom menstruation ceased permanently, did not develop any of the common subjective symptoms of the menopause. Observations mentioned here this morning indicate that in mice treated with radiation a dis-

of the arteriole studied is that above the musculature and in most cases confined to that portion which lies in what Grosser called the "Durchdringungszone." The material has been collected over a period of years by setting aside the routine sections of the placentas which showed vessels. The original material was taken as far away as possible from the margin of the placenta and any sections which showed evidence characteristic of the marginal portion of the placenta were discarded. Only occasional attempts were made to specifically obtain sections through vessels. Fetal vessels entering the decidua were excluded from the study. These retain their muscular walls in contradistinction to the maternal arterioles where formed walls are almost always absent. The fetal vessels pass through this area with surprisingly little change, while the maternal vessels are grossly affected.

Because of the level at which the vessels were studied, it was found impossible to differentiate veins from arteries in most cases. In the vast majority of the vessels found there was great dilatation of the lumen and the vessel wall contained no structures to allow such a differentiation. Spanner<sup>2</sup> has, in a most detailed study, demonstrated the fact that only arterioles penetrate to the upper part of the decidua basalis and enter the intervillous space in the majority of the maternal placental surface, while all venous return occurs through the marginal sinuses which lie in an area within 2 cm. of the circumference. If this be true, as there is every reason to believe, then the vessels with which we are dealing are arterioles. It will be assumed in this paper that this is correct. Stieve<sup>3</sup> makes the bold statement that occasional veins leave the intervillous space through any part of the placenta. The corrosion preparations of Spanner are so convincing that Stieve's unsupported statement is insufficient to throw doubt upon their validity. The studies to be presented show a continuous series of changes in similar vessels. It should be made clear, however, that there is nothing in the structure of these vessels to allow a decision as to their place in the vascular system.

Vessels with intact muscular media are occasionally encountered. These are for the most part small arterioles, and it is suggested that they represent the arterioles given off to supply the decidua and do not enter the intervillous space. Others in the neighborhood of anchoring villi may be readily recognized as fetal vessels.

Changes in the vessels of the decidua basalis have been described by numerous observers and attempts have been made to relate these to ferments or chemical products from degenerating fetal portions of the placenta.<sup>4</sup> The older literature is covered by Grosser<sup>5</sup> who also reproduces photomicrographs of some of the lesions to be described.

The arterioles which conduct blood to the intervillous space show, at the level described above, extensive coiling. Many cross-sections of the same vessel are to be seen in a single section. In the vast majority there is no evidence of a muscular media or an adventitia, and the wall is composed solely of decidua, chorionic cells, a mixture of these in various stages of degeneration or a peculiar hyaline acellular, ground-substance-like material which has been called fibrinoid and which stains densely pink with eosin. The wall of the arteriole, then, does not have the

## VASCULAR LESIONS IN THE DECIDUA BASALIS\*

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THE condition and function of the maternal vascular system in pregnancy is constantly attracting more attention. Information is now available which demonstrates gross disturbances in this system in normal pregnancy. The mechanism by which this is brought about is not as yet clear. Nor is there a proved explanation of the reason for the extension of this disturbance to the degree of the production of a pathologic state in a minority of individuals and its absence in the majority, although hereditary factors seem to partially explain certain types of response, such as the production of arteriolosclerosis. The end results of permanent arteriolar damage<sup>1</sup> are understood and have been demonstrated to be indistinguishable from those of essential hypertension occurring without the pregnancy factor. The etiology of the acute toxemias, i.e., pre-eclampsia and eclampsia, is still far from solution. Two of the fundamental features of these disturbances, edema and hypertension, are related to vascular function. All of this suggests the value of studies of the vascular system in both normal and abnormal pregnancies.

The morphology of the vessels near the placenta is of interest, but one must be cautious in interpreting these findings into generalizations for the vascular system as a whole. Due to the absence of capillaries between the arterial and the venous circulations in this area, special circumstances are present which might be expected to have results similar to those about an arteriovenous fistula.<sup>6, 7</sup> In the second place, it has been assumed that vascular lesions here are associated with continuous exposure to excessive concentrations of toxic substances formed in the fetal portion of the placenta.<sup>4</sup> It has recently been shown that these vessels are arterioles. No one has as yet demonstrated a back flow of intervillous space blood into these arterioles and until such time as this is proved, it might be wiser to assume a continuous blood flow in the direction of the intervillous space.

It is, however, from the vessels of the decidua basalis that that part of the hemorrhage arises which lifts off the placenta from the uterine wall in premature separation of the normally implanted placenta. Curiously enough, no one seems to have given any attention to the question as to whether this hemorrhage is arterial or venous in origin. Disturbances in the vessels here have been described<sup>4</sup> but these descriptions have been incomplete.

The object of this study is to report upon the findings in the arterioles of the decidua basalis in normal and a few abnormal pregnancies. Since the material has been obtained from sections of placentas, the portion

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tions (Fig. 1) of portions of the circumference with splitting of the fibrinoid material into separated layers occur frequently. All degrees of this dilatation are seen until premature separation of the placenta occurs (Fig. 6) when enormous dilatation may be demonstrated.

There is no evidence that this lesion is necessarily associated with clinical evidence of toxemia. For practical purposes all of the material studied was from the placentas of clinically normal pregnancies. The exceptions are noted. Nor is there any evidence of excessive so-called infarction of the placenta in the immediate neighborhood of these lesions.



Fig. 3.

Fig. 3.—Arteriole from the decidua basalis of normal pregnancy. Laying down of fibrinoid material in the wall. Extensive round cell infiltration into the surrounding decidua.  $\times 65$ .



Fig. 4.

Fig. 4.—Arteriole from the decidua basalis of normal pregnancy. Marked dilatation and coiling of the vessel. The portion of the vessel seen in the center shows splitting of the fibrinoid wall with pools of blood plasma.  $\times 65$ .

If, as Spanner states, these are arterioles, there is little reason to assume a retrograde flow from the intervillous space. Under these circumstances the blood bathing the arteriolar wall is general systemic blood and not that from the intervillous space.

These lesions are not limited to the placenta at term. Grosser states that they occur in early pregnancy and they have been found in this series as early as the seventh month. No evidence has been found to prove that invading chorionic epithelium has an etiologic relationship, though this is possible. Occasionally, chorionic cells are seen attached to the wall in the lumen and they may, of course, surround the vessel. The concentric arrangement of the fibrinoid material strongly suggests a central origin.

However, it is clear that the vessels at this level, which are apparently arterioles, are damaged in normal pregnancy. The damage is associated with the laying down of fibrinoid material in the wall. That this is not

supporting structures usual to the arteriole elsewhere. The majority of vessels at this level show advanced degrees of replacement of the cellular surrounding structures by the peculiar fibrinoid material.

This fibrinoid material has a concentric distribution which is unmistakable. It forms rings of varying thickness about the vessel lumen. It may have a well-defined margin against the surrounding cells, but most often connects directly with a similar appearing substance which spreads out in a network between the decidual or chorionic cells and may become continuous with the massive collections of similar substance just beneath the intervillous space. This material in the vessel wall gives the impression of being solid substance. Fibrils are not seen. The surrounding cells may show no evidence of degeneration.



Fig. 1.



Fig. 2.

Fig. 1.—Arteriole from the decidua basalis of normal pregnancy. There is dilatation, laying down of fibrinoid material in the wall and aneurysmal dilatation at one portion. Note the concentric arrangement of the fibrinoid material and the generally sharp line of demarcation between this material and the surrounding decidua.  $\times 65$ .

Fig. 2.—Arteriole from the decidua basalis of normal pregnancy. Enormous dilatation with early aneurysmal dilatation and early thrombosis.  $\times 65$ .

In other vessels the surrounding area appears to be diffusely infiltrated by a plasmalike material which invades peripherally and destroys the enmeshed chorionic or decidual cells. This seems to decrease in concentration and necrotizing influence as it proceeds further from the vessel.

The endothelium of the vessel is most often absent in the vessels at this level at term. The greater the degree of change in the vessel wall, the less endothelium is seen. Occasionally, areas of round cell infiltration (Fig. 3) or massive necrosis of the decidua are seen. These are not typical of the lesion.

The lumina of these vessels are very large (Fig. 2). That this dilatation does not represent a physiologic response seems evident from the character of the vessel wall and from the fact that aneurysmal dilata-

It is extraordinarily difficult to get satisfactory sections for study of the vessels in fully developed premature separation of the normally implanted placenta. There is widespread infarction with destruction of tissue which leads to poor staining. Fig. 6 shows the remains of such vessels from a small area of premature separation. One may be seen to open into the main blood mass producing the separation. The vessels are greatly dilated as those described above and show remnants of the fibrinoid material. There is overlying compression of the villi with early infarct formation, but whether this is related as cause or effect is open to doubt. Under any circumstances the vascular form appears to be similar to that described above.



Fig. 5.



Fig. 6.

Fig. 5.—Arteriole from the decidua basalis of normal pregnancy. Grossly this presented as a small brownish area on the maternal surface of the placenta. On one side may be seen early infarct formation. On the other, there is a mass of fresh blood which has indented the maternal surface. Between these the decidua has been destroyed and the dilated vessels have collapsed. This represents the condition described as miniature premature separation of the normally implanted placenta.  $\times 65$ .

Fig. 6.—Decidua basalis from the margin of a small area of premature separation. The main blood mass is seen and above it, the remains of a vessel at or very close to the area of rupture.  $\times 65$ .

Thus there appears to be a series of changes which occur in what are presumed to be arterioles in the upper portion of the decidua basalis. These begin with replacement of the wall and endothelium by fibrinoid. Gradually, dilatation of the lumen and extension of the fibrinoid with increase in the coiling of the vessel lead to rupture. Blood is extruded. Depending upon the amount of this hemorrhage, varying degrees of premature separation occur. The smallest of these produces a condition described as miniature premature separation. This produces no clinical symptoms. It offers the best available material for the study of the mechanism of premature separation. Larger hemorrhages lead to clinical premature separation.

an efficient structure is manifested in the great dilatation of the lumen and the appearance of aneurysmal dilatations with breaking up of the wall at this point.

The dilatation of the apparently weakened vessel is a dangerous process and the question of its mechanism naturally arises. It occurs in the absence of an increased systemic pressure. It is possible that it represents a response to normal pressure in a weakened vessel. One other explanation is suggested as a likely cause. Burwell and his co-workers<sup>6, 7</sup> have drawn attention to the fact that the intervillous space is a modified arteriovenous fistula. No capillaries are interposed between the arterial and venous circulations. That this arteriovenous fistula effect is modified is shown by the absence of sudden elevations of systemic pressures at delivery when the fistula is removed. Many other changes in pregnancy as increased blood volume, the placental bruit, and increased venous pressure in the lower extremities are suggestively similar to those occurring in clinical or experimental arteriovenous fistula.

In the presence of an arteriovenous fistula there is a readily understandable dilatation of adjacent veins. Halsted<sup>9</sup> pointed out that there was also a dilatation of the proximal artery. The literature is covered by Holman.<sup>8</sup> The mechanism of this is unexplained. The similarity of the result here and in the vessels of the decidua basalis was pointed out by Burwell, and while it is not proved, the author is inclined to accept this as a likely relationship. No exact morphologic studies of the vessels in the region of an experimental or clinical arteriovenous fistula can be found in the literature so that nothing can be said of the relationship between the modified arteriovenous fistula and the deposition of the fibrinoid material in the arteriolar walls.

This dilatation of the arteriole may proceed to great lengths. Fig. 4 shows the vessels from a placenta at term in a normal, nontoxemic pregnancy. The villi adjacent to it show no evidence of infarction. There is normal decidua basalis on either side. The vessels are twisted and enormously dilated. The whole wall is composed of fibrinoid material and contains neither decidua nor chorionic cells. No endothelium remains in the vessels. That portion of the vessel whose whole circumference is seen in the center of Fig. 4 shows its walls to be torn apart by blood plasma which has collected in small lakes. The blood in the lumen shows no evidence of thrombosis.

A further stage of this is seen in Fig. 5 which is also derived from the placenta of a normal term pregnancy. This presented a small reddish brown nodule on the maternal surface of the placenta. On section it shows greatly dilated vessels whose walls are made up of fibrinoid and are ruptured. Old, partly hemolyzed blood lies in the fibrinoid material surrounding the vessels. Immediately above this area the villi are packed together, are relatively avascular, and their epithelium is proliferated. Immediately below is a small collection of blood which lies free beneath the tissue. This represents what might be called a sub-clinical or miniature premature separation of the normally implanted placenta.

When one considers the comparatively fragile attachment of the placenta to the uterine wall, it is surprising that we do not more often see evidences of recent or old separation of the placenta when the specimen is examined. If the structural changes mentioned, predisposed to hemorrhage to the extent claimed by the author, it would seem that clinical degrees of separation of the placenta would occur much more often than is actually the case, and there would be a notable absence of associated toxemia. On the contrary, there has always been emphasized a strikingly frequent association of toxemia.

It has been my observation, that if one carefully examines the fixed placenta from a case of abruptio placentae, one will almost invariably find an area of black or brown acute infarction on or just beneath the maternal surface, where the maternal clot has indented the placental substance. The evident age of the necrosis in the infarct, in contrast to that of the fresh hemorrhage, is sufficient proof that the infarction could not have been caused by the hemorrhage.

Theoretically, clinical degrees of hemorrhage in the decidua basalis must result from the trauma, venous engorgement from kinking of the broad ligament of the overrotated uterus, or damage to the maternal vessels from toxic protein split products of acute placental infarction. The first two are rare. The last has been produced experimentally by Hofbauer by injection of histamine in pregnant guinea pigs. The almost invariable finding of acute placental infarction and toxemia with clinical degrees of premature separation of the placenta, leads me to believe that placental infarction is the cause, rather than structural changes in the maternal arterioles.

DR. JAMES RAGLAN MILLER, HARTFORD, CONN.—On reviewing sections of placentas which I have been able to study since reading McKelvey's paper I have been unable as yet to demonstrate the lesions which he has shown. In a recent case of partial premature separation with external bleeding, I could demonstrate blood vessels in the decidua close to the intervillous spaces and distal to areas of hemorrhage which appeared to be on the maternal side of Nitabuch's fibrin layer. These vessels had for walls a definite single layer of endothelium and showed no abnormal changes, and are probably to be classed as venous capillaries.

With the Masson stain, Nitabuch's so-called fibrin layer stains deep red, suggesting that it consists of degenerated decidual cells. In recent years the finer anatomy and histology of blood vessels have developed on the basis of newer technique which should be applied to the study of the vessels of the placenta. Confirmation is needed, for example, of the observation that in the endometrial basal arteries of the nonpregnant uterus, there is an absence of elastic fibers, though they are present both above and below this zone. It is this layer of blood vessels which appears to be concerned in the mechanism of menstruation in the last forty-eight hours before bleeding occurs. It is also this layer of blood vessels in which we might expect to find changes productive of premature separation.

Until the modern methods of study have been applied to the finer histology of the blood vessels involved, it would seem too early to do more than speculate concerning the part which toxemia may play in premature separation, and perhaps, even to speculate on the mechanism of such hemorrhages.

DR. OTTO H. SCHWARZ, St. LOUIS, MO.—Studies made by us in 1923 were from material secured at autopsy before the patient was delivered, or from the placenta obtained by cesarean section. In most cases that had definite hypertension the changes in the inner third of the arterioles were very striking. They showed arteriosclerosis with some destruction of the intima. We also studied the vessels of the basalis and in several instances we saw excessive dilatation with only a strand of the vessel remaining. At that time we suggested that these aneurysmal dilatations might be responsible for some cases of placental apoplexy, but not all. We suggested also that this might result from a marked hypertension that existed in these patients before they died.

DR. MCKELVEY (closing).—Both Bartholomew and Miller have raised the question of the relationship of toxemic effects in the production of disturbances in

Various degrees of these changes occur in the majority of arterioles of the decidua basalis and their occurrence is independent of the presence of the pregnancy toxemias. In the early stages at least, there is no evidence to support an etiologic relationship to infarction of the placenta. Such relationship in clinical premature separation is not yet proved, though possible. The modified arteriovenous aneurysm effect of the intervillous space is again suggested as a causal factor in the production of dilatation of these vessels. Its relationship to the other changes described is not clear.

It is suggested, then, that the basic circumstances inherent in premature separation of the placenta are present in most if not all human placentas. The degree of extension of this process determines the appearance or nonappearance of clinical premature separation.

### CONCLUSIONS

1. In association with normal pregnancy, lesions in the arterioles of the upper part of the decidua basalis frequently occur. These changes include the laying down of fibrinoid material in the wall, dilatation and aneurysmal dilatation. They are not necessarily associated with pregnancy toxemia nor with placental infarcts.

2. A series of these changes may be traced from mild lesions to rupture with the production of miniature or clinical premature separation of the normally implanted placenta.

3. Premature separation of the normally implanted placenta is an extension of changes in the arterioles probably present in every human placenta. One of the factors in this extension is the arteriolar dilatation associated with the modified arteriovenous aneurysm effect of the intervillous space.

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### DISCUSSION

DR. RUDOLPH A. BARTHOLOMEW, ATLANTA, GA.—McKelvey contends there are certain fundamental structural changes and conditions of the maternal arterioles in the decidua basalis which predispose to and cause premature separation of the placenta, not only in subclinical or miniature form but in more severe abruptio or ablatio form. He also contends that such separation occurs without any evidence of toxemia or adjacent infarction.

It seems reasonable to believe that the dilated terminations of the maternal arterioles, the thinning of their walls, the loss of endothelial lining and the presence of the so-called fibrinoid or hyaline substance about the vessels and in the decidua, have existed since the early stage of formation of the placenta, and represent the final result of the interaction of the invasive trophoblast and the maternal decidua and arterioles.

# CHORIOEPITHELIOMA\*

## A CLINICAL AND PATHOLOGICAL STUDY

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CHORIOEPITHELIOMA is ordinarily regarded as one of the most malignant epithelial tumors with which we have to deal, but at the same time it is also a type of tumor which at times presents quite extraordinary vagaries in its growth and general course of development. In considering some of its characteristics, it is interesting to recall that it originates in cells which normally possess highly invasive powers, and which in addition may even be broken off from the developing ovum and be carried by the blood stream as minute cellular emboli to distant parts of the body, the so-called deportation of chorionic villi. How long these invading or transported fetal cells persist after the pregnancy from which they originate comes to an end is unknown. In general, they probably degenerate early, but on the other hand may occasionally persist for a long period of time, even for years, as is evidenced by the development of a chorioepithelioma months or years after an hydatid mole or other form of pregnancy. With these characteristics of normal trophoblastic cells in mind, the wonder is that malignant change does not occur more often than is actually the case.

The series of chorioepitheliomas herewith presented, though small, illustrates rather well both the usual characteristics of this type of tumor and some of the less frequently observed features of this relatively rare type of tumor.

CASE 1.—(Unit No. 35102.) J. G., aged 24 years, para ii, was admitted May 12, 1930 with active vaginal bleeding present for ten days. Hb. 28 per cent, red blood cells 2,000,000. Menstruated last on February 15. Fundus of uterus at the level of the umbilicus. Transfused and hydatid mole removed by vaginal route. No ovarian enlargement noted. Microscopic examination of the tissue removed showed the typical picture of hydatid mole with no appearance of malignancy. June 7 on account of recurrence of moderate vaginal bleeding, curettage was done. Curettings revealed normal regenerating endometrium but also a few microscopic fragments of mole which were not considered malignant. Friedman test positive with 5 c.c. of urine, becoming negative after forty-eight hours. July 15, recurrence of moderate bleeding, diagnostic curettage. Curettings scanty and showed normal endometrium with no fetal tissue. Friedman test negative. Normal menstruation re-established in August and continued so for a year. Aug. 26, 1931 readmitted on account of slight persistent bleeding present for three weeks. General and pelvic examination revealed no abnormalities. Diagnostic curettage done. Curettings scanty and microscopically showed normal endometrium. Oct. 8, 1931, menstruation delayed eight days but then occurred normally. Friedman test negative. Nov. 5, 1931 seen in outpatient department and condition appeared satisfactory. Pelvic

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systemic pressure and its effect in the rupture of these vessels. I can only say that I have no evidence whatever to lead me to any explanation of the relationship between disturbed systemic pressure and the changes in these vessels, although one might of course assume that that occurred. Yet it is always dangerous to accept obvious explanations. Something else is going on, and the changes in the pressure within these arterioles in relation to the changes of the vessels in arteriovenous fistulas would lead one to suspect that here is an area where systemic pressure is at its lowest instead of at its highest. I have no explanation for the incidence of increased pressure, but that that is a well-recognized fact goes without saying. The cases that have worried us are the ones where separation occurs without hypertension.

Bartholomew has referred to the possible relationship of the infarcts. My main object is to present the changes in the vessels in normal pregnancy and those without demonstrable infarction. The first four were taken from areas which showed no morphologic or gross evidence of infarction around those regions. In my opinion, the age of the infarction in premature separation, and the presumption that it preceded the vascular lesion are open to some doubt, but we cannot rule out an infarction effect as a final throwing over of a potential vascular lesion into a clinical lesion.

Miller had my paper for only a short time, and it is a fact that one may search many sections without finding any vessels. My material has been collected over a period of four to six years, during which time we simply put aside those sections which do show vessels. I have somewhere in the neighborhood of a couple of hundred in which the vessels demonstrate lesions.

It is also true that there is no necessary relationship between the degree of the lesions in various vessels of the same placenta. This peculiar spotty effect of vascular lesions is characteristic of arteriolosclerosis that is seen elsewhere in the body, and I believe that we have here a similar effect. There appears to be an element of chance in these lesions. The fact that there is a premature separation in some vessels is not evidence that there will be destruction of other vessels.

The paper Schwarz spoke of, as I remember, dealt primarily with the vessels of the uterine musculature and not those close to the entrance into the intervillous space. The vessels in the upper part of the decidua basalis have no wall of any sort except endothelium and a basal membrane.



direct extension of the growth and dissemination throughout the peritoneal cavity occurs as a result of this. Under such circumstances too there may be a fatal intraperitoneal hemorrhage. This mode of extension is well illustrated in the second case in this series.

CASE 2.—(Unit No. 20593.) F. D., aged 38 years, para ii, grav. v. Admitted Dec. 27, 1928. In September, 1928 had completion of a two months' spontaneous, incomplete abortion in another hospital. Discharged after five days. Following this had irregular episodes of bleeding with a profuse hemorrhage on December 1.

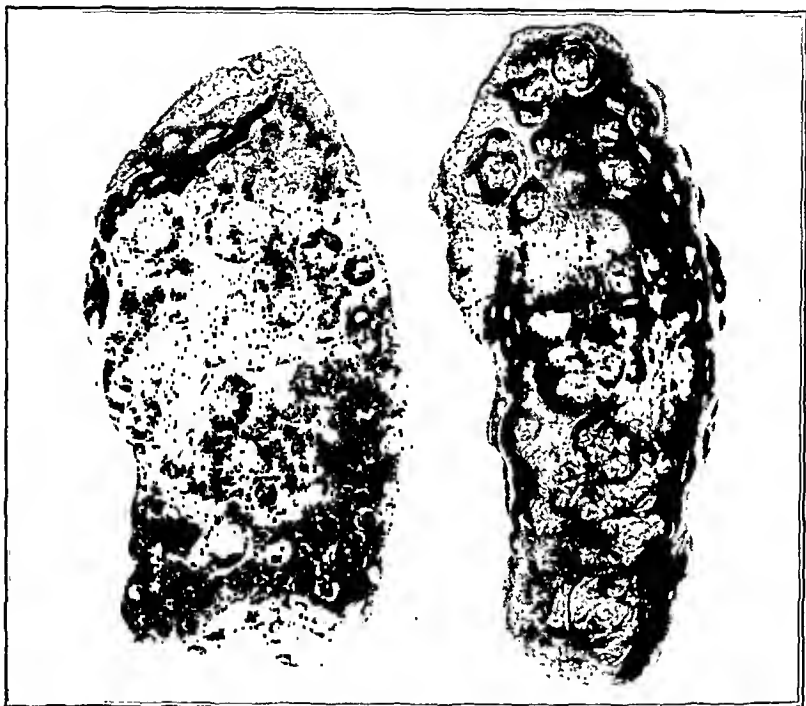


Fig. 2.—The lungs from Case 1 showing extensive nodular metastases.



Fig. 3.—The microscopic picture of the uterine tumor from Case 1 shows active growth of both types of cells.

examination negative. December 26 admitted to hospital, critically ill, with history of cough and bloody sputum for the past week. In addition a rounded tumor nodule 4 cm. in diameter discovered in anterior vaginal wall. Radiograph of chest showed extensive metastatic involvement of both lungs. Friedman test positive with 5 c.c. of urine. Died Dec. 30, 1931. Autopsy showed chorioepithelioma of uterus with metastases to vagina, lungs, and kidneys. No lymph node involvement.

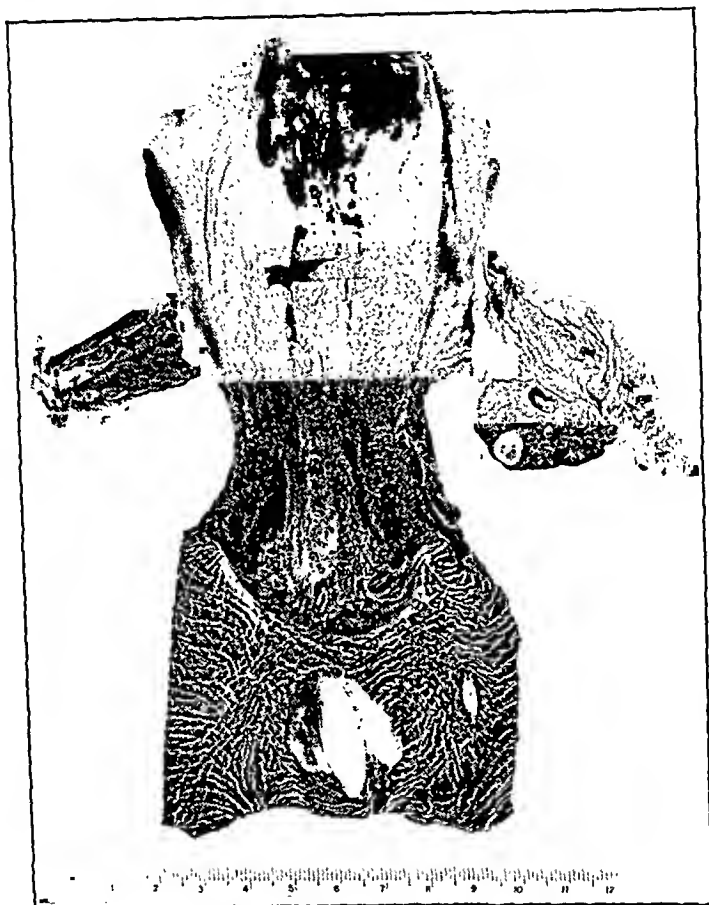


Fig. 1.—Pelvic organs removed from Case 1 at autopsy. The uterine tumor is embedded in the wall of the uterus and is covered by normal endometrium so that a diagnostic curettage would be very misleading. The curette would remove no tumor tissue unless it were thrust deeply into the tumor mass. Note the vaginal metastases.

*Comment.*—Unless this tumor followed the unusually rapid course of two and one-half months from beginning to end, we are forced to the conclusion that the result of the Friedman rabbit ovulation test was not only of no help from the diagnostic standpoint, but was actually misleading, as a negative result was obtained at a time when it seems reasonable to suppose that this woman harbored an actively developing tumor though presenting no clinical signs or symptoms.

Chorioepithelioma being a highly vascular tumor, with numerous blood spaces within it, ordinarily metastasizes by the blood stream, hence secondary lesions about the vagina or vulva, or in the lungs, are frequently seen. At the same time, as the cells possess such highly invasive properties, the uterine wall may be actually perforated as the result of

operation was obviously useless, so a subtotal hysterectomy with removal of both appendages was carried out as a purely palliative measure to prevent further bleeding. Microscopic examination of the tumor showed the characteristic appearance of a rapidly growing chorioepithelioma, with no significant ovarian changes noted. Postoperative convalescence uneventful. Deep x-ray therapy carried out as a further palliative measure. February 5, radiograph revealed metastatic area in right lung; deep x-ray therapy directed towards this. March 26, extension of pulmonary lesions observed but no subjective symptoms. April 30, cough with bloody expectoration, rapid downhill course, and died at home June 3, 1929. No autopsy.

Among the peculiarities of this type of tumor is the fact that at times no primary uterine tumor may be demonstrable, and yet single or multiple growths may be found in other parts of the body and cause death. In explaining the origin of these so-called "ectopic chorioepitheliomas," apart from their occasional teratomatous origin, several possibilities must be considered. According to Schmorl, such an ectopic tumor might arise from an hydatid mole or other form of pregnancy in which a malignant change had taken place in some of the trophoblastic cells, possibly in only a very small area of the placenta, before the ovum was expelled or removed from the uterus. These malignant cells if transported elsewhere by the blood stream, could obviously become metastatic growths, and yet no tumor would be found in the uterus. Marehand, Pick, and others believe that these ectopic tumors may arise as the result of malignant change in the trophoblastic cells transported to other portions of the body in the course of a perfectly normal pregnancy. Still another possibility in regard to the origin of the ectopic tumor is to be found in the case presented by Novak and Koff in which the primary uterine tumor disappeared but the patient died as the result of metastases. A most unusual example of ectopic chorioepithelioma is that reported by Sears in which the tumor was located in the jejunum, and developed nearly three years after the last probable preceding pregnancy.

CASE 3.—(An example of ectopic chorioepithelioma.) (Unit No. 106899.) E. S., aged 28 years, para ii. Admitted Sept. 15, 1935 after a sudden onset of cerebral symptoms, headache, vomiting, irrational. Lumbar puncture showed blood in cerebrospinal fluid. Last pregnancy a normal full-term delivery one year previous to admission. One year prior to that a possible mole removed from uterus. For six months prior to admission there had been slight persistent vaginal bleeding but no marked anemia developed. Pelvic examination revealed a slightly enlarged retroverted uterus, ovaries not enlarged. Radiograph of chest negative. September 17 and September 27 Friedman test positive with 5 c.c. of urine. September 28, diagnostic curettage. The curettings presented an appearance suggestive of decidua and yet not typical. No trophoblastic cells were found. On the basis of the positive Friedman test together with the other clinical findings, a tentative diagnosis of chorioepithelioma of the brain was made. Oct. 4, craniotomy and decompression (Dr. Van Wagenen). The general condition improved following the decompression, and she was discharged on October 19. Friedman test remained positive. Died at home Nov. 3, 1935. Autopsy showed chorioepithelioma of brain, lungs, spleen, and kidneys. No evidence of tumor formation in the uterus and no significant findings in the ovaries.

*Comment.*—In this ectopic chorioepithelioma, it is impossible to say definitely whether there had been a primary uterine tumor which dis-

## WILSON: CHORIOEPITHELIOMA

Uterus and vagina packed by her physician and at the same time some tissue obtained for examination which showed definite chorioepithelioma. On admission to our service Hb. 50 per cent, red blood count 2,770,000. Radiograph of chest negative. Pelvic examination showed uterus enlarged to the size of a two months' pregnancy, but freely movable, slight bleeding, no ovarian enlargement. Transfusions given and other antianemic therapy. January 7 operation. On opening the abdomen considerable chocolate colored material escaped and numerous adhesions were encountered. When the uterus was exposed, a small friable bleeding nodule was found at the left uterine cornu, evidently a direct extension of the tumor through the uterine wall. As there were extensive peritoneal implants, a radical

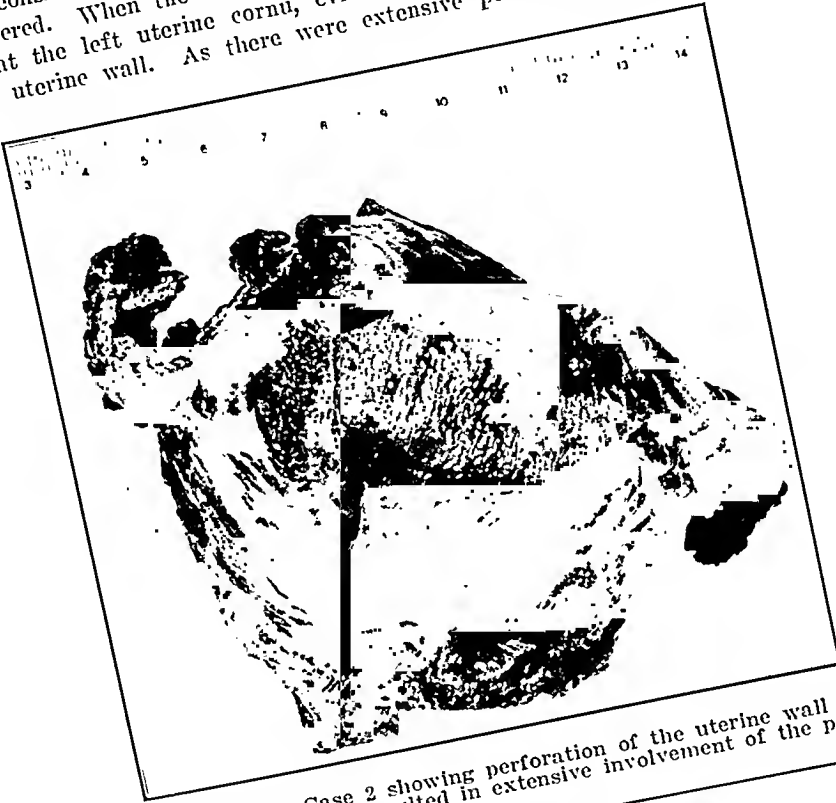


Fig. 4.—The uterus from Case 2 showing perforation of the uterine wall by extension of the tumor growth. This resulted in extensive involvement of the peritoneum.

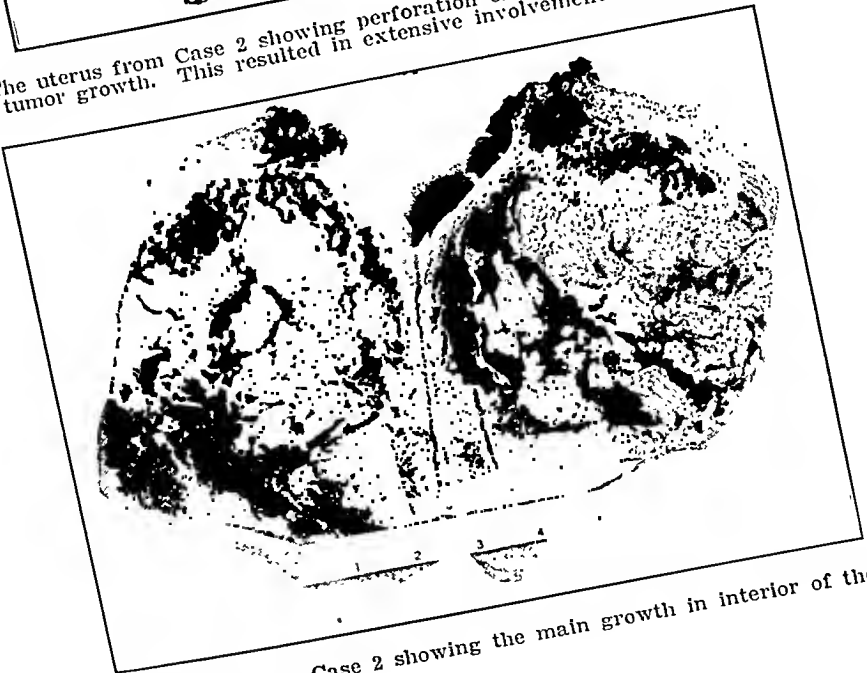


Fig. 5.—The uterus from Case 2 showing the main growth in interior of the uterus.

Microscopic examination of the tissue revealed some typical hydatid vesicles, but in addition such extensive proliferative changes were noted in some of the trophoblastic masses involving in particular the Langhans cells that the additional diagnosis of chorioepithelioma was made. August 14 chest and skull radiographs negative. August 21 total hysterectomy. On opening the uterus after its removal, a

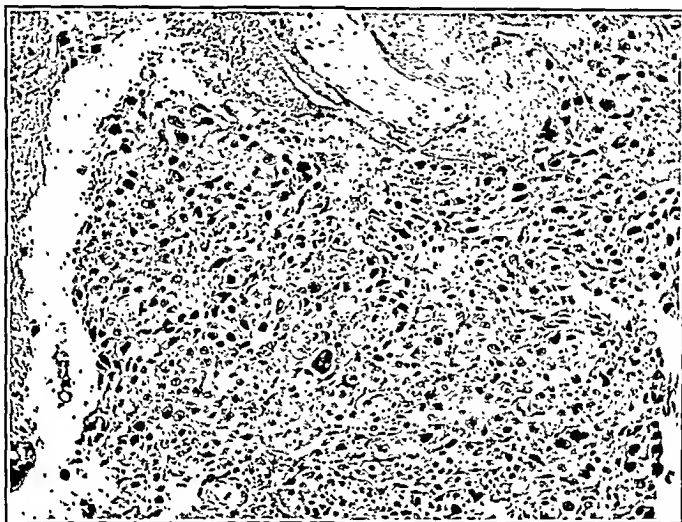


Fig. 8.—Microscopic picture of a fragment of the mole from Case 4 on which a diagnosis of chorioepithelioma was based. Note the extensive and irregular proliferation, with anaplasia, involving in particular the Langhans cells.



Fig. 9.—Microscopic picture of the uterine tumor from Case 4. Note both types of cells surrounding large blood spaces. The tumor is embedded in the uterine wall and is partially covered by endometrium which shows relatively normal glands.

reddish tumor mass about 2 cm. in diameter was found in the fundus. This had invaded the uterine wall to some extent. Microscopic study revealed a typical picture of chorioepithelioma with both of the usual types of cells included in its structure. Postoperative convalescence uneventful, and her condition today is excellent.

Repeated observations on the Friedman rabbit ovulation test were made on the urine of this patient and gave rather interesting results both from the diagnostic

appeared after metastases had developed, or whether it was an ectopic tumor from the beginning, developing from trophoblastic cells transported during one of her previous pregnancies.

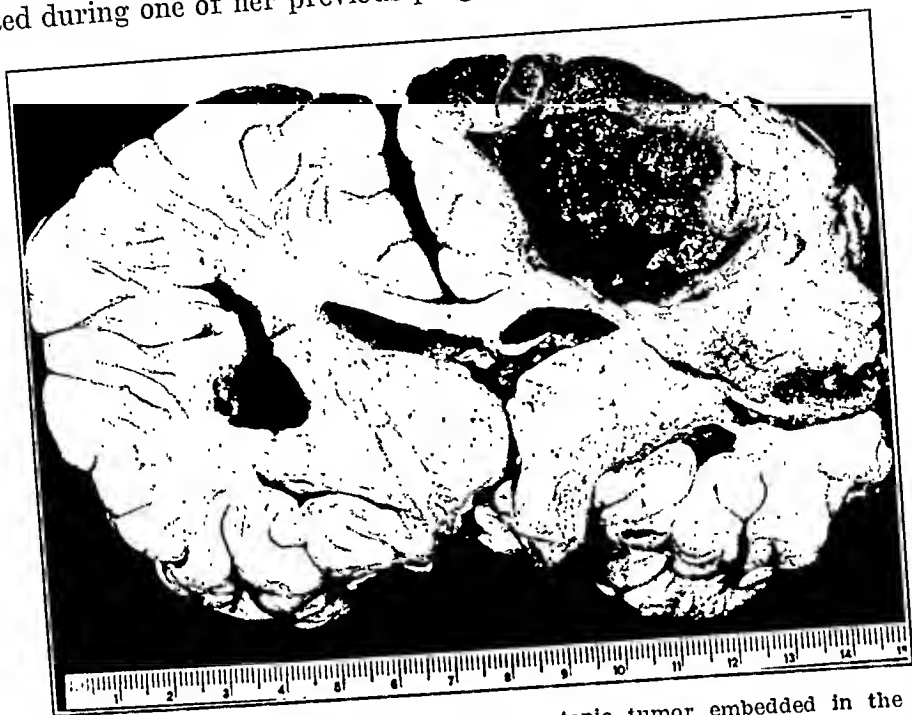


Fig. 6.—The brain from Case 3 showing the ectopic tumor embedded in the brain substance.

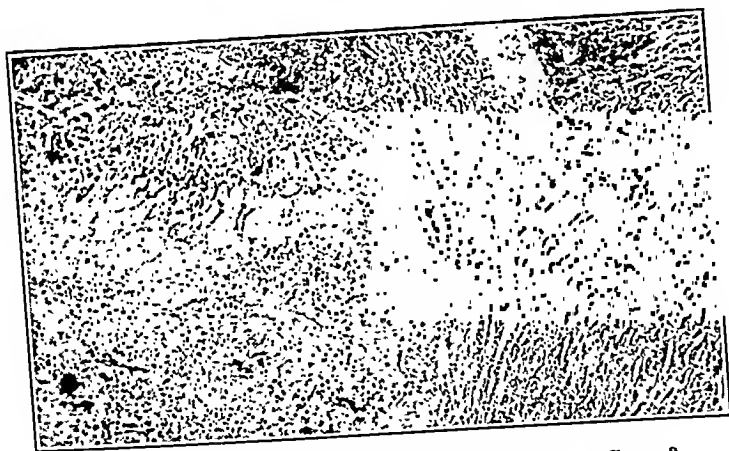


Fig. 7.—A metastatic growth in the kidney of Case 3.

CASE 4.—(Unit No. 80606.) F. S., aged 27 years, para i, gravida ii. Admitted July 28, 1936. Last menstrual period April 4. Uterus the size of a three and one-half months' pregnancy, and a large cystic mass discovered adjacent to it. Friedman test positive with 5 c.c. of urine. Diagnosis: Pregnancy with ovarian cystoma. August 1 laparotomy, bilateral cystomas discovered and removed. Uterus of a size corresponding to period of amenorrhea. The cystomas proved to be multilocular "lutein" cystomas. It is interesting to note that embedded in one of these a normal appearing corpus luteum, 3 cm. in diameter, was found. A belated tentative diagnosis of hydatid mole was made. Two days after operation vaginal bleeding and uterine cramps occurred. August 8 removal of hydatid mole, some of the tissue grossly typical, but much of it necrotic and foul smelling.

## DISCUSSION

This small series illustrates many of the usual features in connection with chorioepithelioma as well as some of the less frequently encountered variations. Two of the tumors were preceded by hydatid mole, two by abortions, and one by a full-term pregnancy. Fairly wide variations in the time elapsing between the occurrence of the original pregnancy

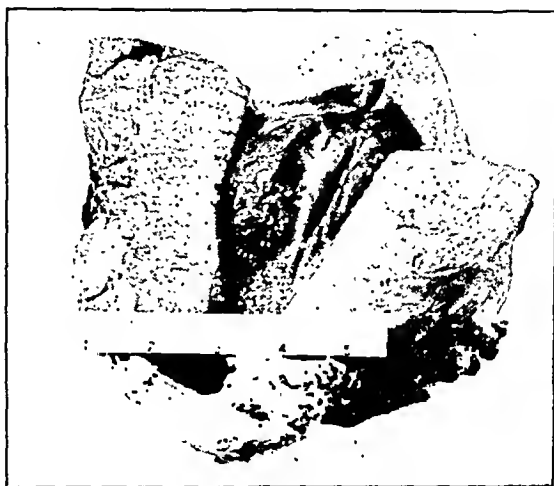


Fig. 11.—The uterus from Case 5 with a partially pedunculated tumor near the fundus.

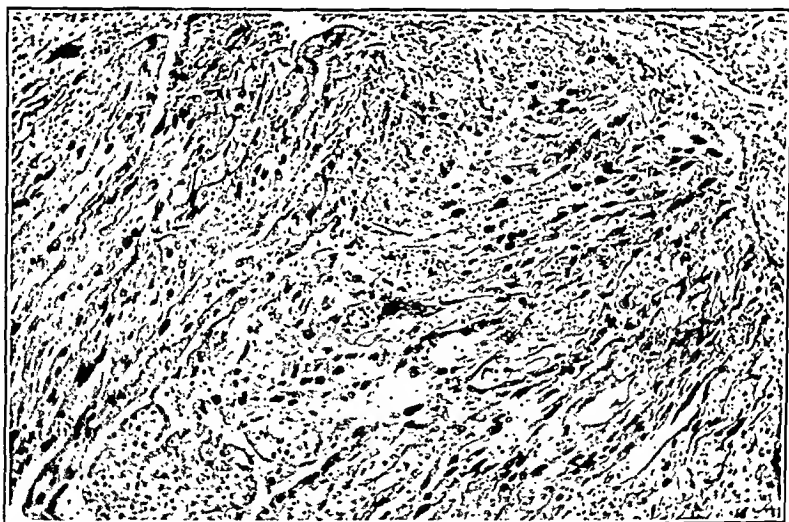


Fig. 12.—Microscopic picture of the tumor from Case 5. Note active proliferation of both types of cells, and yet the almost complete absence of invasion of the uterine wall beneath the main tumor. Adjacent to this, however, are small areas which show some invasion of the uterine wall.

and the development of the malignant tumor are also observed. Thus the time range varies from immediate occurrence as in Case 4 to more than a year in Case 1. Two have survived for one and three years, respectively, while the other three died.

The diagnosis of chorioepithelioma is at times an extremely easy one to make, but on the other hand, it may tax the resources of the most

as well as the prognostic standpoints. July 28 reaction positive with 5 c.e. After the possibility of hydatid mole was suspected, it was done fractionally and a positive result obtained on various days before the removal of the mole with such small amounts of urine as 0.10, 0.08, and 0.05 c.e. August 13 (after removal of mole) Friedman test positive with 5 c.e. of urine. August 30 (twelve days after hysterectomy) reaction negative with 7 c.e. November 10 reaction positive with 7 c.e. Pelvic examination at this time showed no gross abnormalities and radiograph of chest was negative. Fearing the possibility of a recurrence, she was given deep x-ray therapy to the pelvis through six portals, total dosage 6,600 r. units. Following this the Friedman test became negative and has remained so to date even with as much as 15 c.e. of urine.

*Comment.*—This is the only patient in our series who showed striking ovarian changes in association with her tumor.

CASE 5.—(Unit No. 140365.) A. K., aged 45 years, para ii. Admitted May 10, 1938. Probable miscarriage at about two months in February. Bleeding continued up to time of admission. On admission Hb. 6 gm., red blood count 2,400,000. Transfusions given. Diagnostic curettage done May 18. Microscopic diagnosis chorioepithelioma. After curettage Friedman test positive with 5 c.e., and 0.5 c.e. of

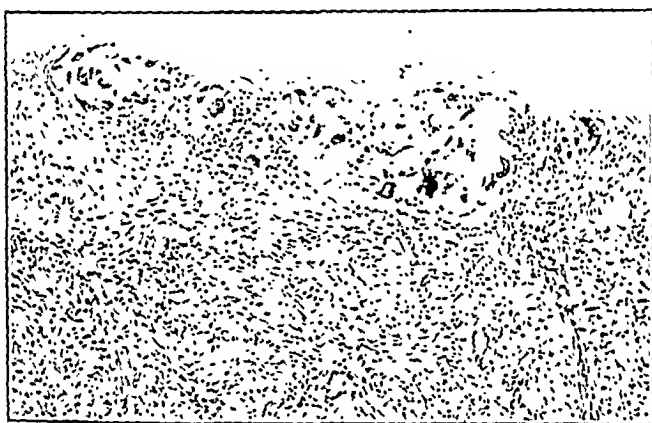


Fig. 10.—A small collection of tumor cells on the surface of the uterus in Case 4, but still covered by a very thin peritoneal layer.

urine but negative with 0.1 c.e. May 26 operation, panhysterectomy and removal of both appendages. The uterus was a little larger than normal and contained numerous seedling myomas. On opening it a reddish, partially pedunculated tumor 4 cm. in length was found near the fundus. On incising the base of this, there was no gross evidence of invasion of the uterine wall. Postoperative convalescence was uneventful, and her present condition, a year later, is excellent. June 1 (six days postoperative) Friedman test positive with 5 c.e. of urine. June 5 (10 days postoperative) Friedman test negative with 9.0 c.e. of urine, also in successive observations, the last one being Mar. 8, 1939 with 10 c.e.

*Comment.*—It seems not unlikely that in this case we were dealing with malignant change in a retained fragment of placental tissue remaining after the miscarriage occurring three months previously. There was minimal invasion of the uterine wall, though histologically there was no detectable difference as compared with the other tumors. Biologically, however, there was, and this one was evidently of a lower grade of malignancy. Possibly this might represent also one of the unusual type of tumors which disappear spontaneously.



Zondek test in mice and the Friedman ovulation test in rabbits, so widely used in the diagnosis of pregnancy, are based on the presence or absence of this hormone in the urine of the individual to be tested. Aschheim was the first to draw attention to the fact that in the presence of hydatid mole or chorioepithelioma, this hormone is found in the urine in unusually large amounts, and he suggested the diagnostic and prognostic value of this finding.

The amount of the hormone present in the urine in either of these conditions is likely to be so great as to give a positive reaction when only a fraction of 1 c.c. of urine is injected into the test animal. Aschheim also carried out quantitative estimations of the hormone content of the urine and came to the conclusion that if on bio-assay a liter of urine contained more than 100,000 mouse units of the hormone, the probabilities would be in favor of hydatid mole or chorioepithelioma being present. He also found, however, that the amount varied according to the size of the mole and that in the small degenerated mole the amount of hormone excreted might not exceed that found in normal pregnancy.

The work of Evans and his colleagues would indicate that further reservations are necessary when these tests are used as diagnostic aids. Thus they found that in normal pregnancy there is a transient period usually about the thirtieth day of the pregnancy when enormous amounts of the chorionic gonadotropic hormone are excreted, and in one instance in their series the total daily excretion amounted to 1,000,000 rat units and a positive test was obtained with 0.005 c.c. of urine. Normally, however, this excretion of large amounts of hormone is a transient phenomenon, and after the peak is reached there is a rapid decrease, until after the sixty-fifth day of the pregnancy when the hormone output was found to be below 10,000 rat units per liter, and continued so until the termination of the pregnancy. From the findings of these observers, it is evident that the demonstration of large amounts of this hormone in the urine does not necessarily warrant the diagnosis of hydatid mole or chorioepithelioma. On the other hand, it does necessitate a careful correlation of the laboratory studies and the clinical findings.

Aschheim states that if the urine of a suspected case gives a negative reaction, chorioepithelioma can be ruled out. That is not entirely correct, as in our Case 1 a negative result was obtained at a time when the tumor must have been developing. The occasional false negative reaction is the chief source of error when these biologic tests are used in the diagnosis of pregnancy, but one would expect such errors to occur less frequently in the case of tumor development. Undoubtedly, greater attention should be paid to the specific gravity of the urine to be tested, as obviously the concentration of the hormone would be less in the urine of low specific gravity. Probably also more accurate information would be obtained by an estimation of the total daily output of the hormone.

With these reservations in mind, it is permissible to say that these biologic reactions may prove to be of considerable diagnostic and prognostic value. Thus a strong positive Aschheim-Zondek or Friedman test, or the demonstration of unusually large amounts of the hormone in a

experienced pathologist. The condition will be suspected in the event of persistent bleeding following an hydatid mole or other form of pregnancy, but the early diagnosis of a uterine tumor can only be established by the microscopic study of material from the uterus obtained by diagnostic curettage. Even this may fail. If the tumor be completely embedded in the uterine wall and completely covered by normal endometrium as in our Case 1, tumor tissue will not be removed by the curette and an erroneous diagnosis will be made. Such a relationship of the tumor will, however, be infrequent. The greatest difficulty will arise in connection with the hydatid mole, in arriving at a decision from the material examined as to whether it is benign or whether malignant change has already taken place. This difficulty arises on account of the unusually active proliferation of the trophoblastic cells of the mole, and there may even be some destructive invasion of the uterine wall. Ewing distinguishes between the benign and the malignant mole and states that the differential diagnosis between the two usually presents no difficulty, a view which it is difficult to accept. To the latter he applies the term *chorioadenoma destruens*, but as Novak and Koff point out, it would seem preferable to regard this as a type of chorioepithelioma, definitely malignant, though of a somewhat lower grade of malignancy than other types. This diagnostic problem arose in connection with our Case 4. The unusual degree of trophoblastic proliferation discovered in the tissue of the mole at the time of its removal and which particularly involved the Langhans cells, together with a degree of anaplasia and nuclear changes not ordinarily seen with an hydatid mole, led us to make the diagnosis of malignancy. Further study of the uterus grossly and microscopically after its removal left no doubt as to the correctness of this diagnosis.

The degree of invasiveness has been suggested as a criterion for determining whether a mole is malignant or not. This is of value, but on the other hand, the nonmalignant mole as well as other forms of trophoblastic tissue may invade the uterine wall to a considerable extent, so that at times it is difficult or impossible to arrive at a correct conclusion. If the diagnosis of malignancy is already established, however, the degree of invasiveness will be of great value in grading the tumor as to its degree of malignancy. Thus in Case 5 in our series when minimal invasion of the uterine wall was observed, we had no hesitation in making the diagnosis of chorioepithelioma, but also felt that it was a tumor of relatively low grade malignancy. Possibly a more highly invasive power would have developed later. Unfortunately, the degree of invasiveness cannot be determined until we have the opportunity to study the tumor in situ after the uterus has been removed, so this criterion cannot be used as a diagnostic aid when we are trying to establish a diagnosis from curettings.

One of the interesting biologic reactions of both the hydatid mole and chorioepithelioma is seen in their production of large amounts of the gonad-stimulating hormone somewhat similar in its action to that produced by the anterior lobe of the hypophysis and probably identical with that produced by the ovum in a normal pregnancy. The Aschheim-

I have never seen the wisdom of describing an intermediate group, such as the chorioadenoma destruens of Ewing. The malignant characteristics attributed to this group entitle them to inclusion under the designation of chorioepithelioma, though of a lower degree of malignancy than some other types.

DR. BROOKE M. ANSPACH, PHILADELPHIA, PA.—I have observed three cases of chorioepithelioma, each with certain interesting features which apply to the subject matter of Wilson's paper.

CASE 1.—A young woman, in her first pregnancy, had pernicious vomiting. A hysterotomy was performed for hydatidiform mole, and the left ovary, which was cystic and adherent in Douglas' pouch, was removed. Three months later uterine bleeding developed. A curettage revealed proliferating chorionic tissue, but the pathologist was unwilling to make a diagnosis on the histology alone. In the course of three weeks the patient developed a tumor the size of an egg in the left lateral wall of the uterus. At the time of the hysterotomy both ovaries had been enlarged to the size of apples, but at the time of the panhysterectomy in May, the right ovary was reduced to almost less than the average size. This patient is now in excellent health, so that the tumor evidently was of the more benign type. Her first operation had been in January, 1926.

CASE 2.—The patient had had an abortion two months before an acute episode in which she suddenly developed great abdominal pain, difficulty in speech and partial right-sided paralysis. She was evidently losing blood at a rapid rate internally, and the pelvic findings, though inconclusive, suggested a ruptured ectopic. The chorioepithelioma occupied the anterior wall of the uterus and was entirely outside the uterine cavity. The patient recovered, and the aphasic and hemiplegic symptoms grew less. The neurologists were not able to find any evidence of organic brain lesion, so that the cerebral symptoms were ascribed to the loss of blood. The patient is still alive and well.

CASE 3.—This patient, the mother of four children, came in 1935 to Jefferson Hospital with a tumor embedded in the anterior vaginal vault presenting and at the vulvar orifice. There was no evidence of metastasis, and we treated her at first with deep x-ray therapy, which caused the vaginal tumor to shrink rapidly. We got in this case a very decided Friedman reaction from 1/100 c.c. of urine. The vaginal growth later recurred and metastases appeared in the lungs. Removal of the uterine tumor was followed by death within a couple of weeks. The nodules were in the uterine wall and not in the uterine cavity, so that there was no uterine bleeding. This evidently was a chorioepithelioma of the very malignant type.

DR. RAYMOND E. WATKINS, PORTLAND, ORE.—Our experience consists of four epitheliomas in the last twelve years, three of which followed hydatidiform mole and the fourth a full-term pregnancy. The first three patients are alive, without recurrence; one 18 months, one 2 years, and one 12 years. The fourth, after full-term pregnancy, is dead.

I should like to present a short history of the last case. A white female, 29 years old, para iv, at term, entered the obstetric ward of the University of Oregon Medical School on March 11, 1936. Her complaint was painless bleeding. A diagnosis of marginal placenta previa was made and labor induced. After five hours she delivered a normal living child without further hemorrhage. The placenta was expelled almost immediately and showed fibrosis at one margin. Her convalescence was normal except that on the third day she passed a clot 10 cm. in diameter.

Thirty-six days after delivery, following a severe uterine hemorrhage, she re-entered the hospital in profound shock. At curettage, considerable friable tissue resembling placenta was recovered, and the pathologic diagnosis was probable chorioepithelioma.

The Friedman test was positive. Chest plates were negative. Nine days later, the forty-fifth day post partum, a panhysterectomy was done. A round, purplish gray growth 1.5 cm. in diameter projected into the endometrial cavity from the posterior wall of the uterus. Microscopic sections were diagnosed chorioepithelioma.

twenty-four-hour specimen of urine may be helpful in establishing a diagnosis of hydatid mole or chorioepithelioma, provided due consideration be given to the associated clinical findings. These procedures will not, however, enable one to differentiate between the benign mole and the malignant tumor. Persistence of a positive reaction after the removal of a mole or tumor would strongly suggest that the removal had been incomplete or that metastases had occurred, while if a previously positive reaction becomes negative after operation, the assumption would be that the tumor had been completely removed. Repeated observations should be carried out, though, as this may give us the first clue as to a possible recurrence. In our Cases 4 and 5, it was found that the reaction became negative ten and twelve days after operation, respectively. Again, the appearance of a positive reaction, after it had previously become negative, would strongly suggest a recurrence of the tumor.

#### SUMMARY

Five examples of chorioepithelioma, including one ectopic tumor, are presented. These show variations in their mode of development and extension.

The diagnostic and prognostic value of the biologic reaction in connection with these tumors is discussed.

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#### DISCUSSION

DR. EMIL NOVAK, BALTIMORE, MD.—Much stress is being laid on the importance of biologic tests which, although of real value in both diagnosis and prognosis, have their limitations. They will not, for example, distinguish between a benign hydatidiform mole and the malignant chorioepithelioma. The final diagnosis, which alone justifies the report of a case as chorioepithelioma, must be based on the microscopic examination of the tumor. In a recent paper, the statement was made that now since we have available these biologic methods of study, the mortality of chorioepithelioma should be reduced to 5 or 10 per cent, a very far-fetched statement utterly at variance with what we know as to the clinical course.

I need not remind you of the difficulties of microscopic examination in some cases. If a well-preserved villous pattern is found in tissue curetted from the uterus, one should lean backward before making the diagnosis of chorioepithelioma, even though there is much trophoblastic proliferation. On the other hand, when one finds large masses of anaplastic trophoblastic tissue without villi, no other diagnosis than chorioepithelioma would seem justified.

In cases of hydatidiform mole, the vesicles evacuated spontaneously or surgically from the uterine cavity, well away from their blood supply, may seem obviously benign, with little or no trophoblastic activity. A section of the same mole in situ in the uterine wall, will always show much more activity, so that, even though benign, it may be mistaken for chorioepithelioma. Such cases, however, commonly lack the destructive invasion of the uterine muscle by large masses of trophoblast, with the death of the muscle by coagulation necrosis, which characterizes the chorioepithelioma.

One patient, aged 51 years, came in with vaginal bleeding from a vulvar lesion. A year and a half previously she had been operated upon for ectopic pregnancy. She developed extensive pulmonary involvement and died within three months from the first symptoms. In our experience the choriocarcinoma patients die on an average of five months from the time of the onset of symptoms.

A second patient was also operated upon for ectopic pregnancy. The uterus was subsequently removed because of the pathologic report. Sections showed not only ectopic pregnancy, but also choriocarcinoma. This patient returned with a recurrence in the pelvis and a metastasis in the upper right lobe of the lung. This is the only patient in our series in whom the tumors disappeared under radiation therapy, and she has remained alive now three and a half years since the onset of her disease.

DR. WILSON (closing).—In preparing this paper I was interested to see that only once before in the history of this Society has a paper on this subject been presented, namely by Dr. Vineberg in 1918.

Dr. Novak very properly emphasizes the problem of microscopic diagnosis. Yet I would emphasize that even here difficulty is often encountered in deciding whether a given hydatid mole has become malignant or not. There is practically always unusually active epithelial proliferation even in connection with the benign hydatid mole.

I do not wish to overemphasize the biologic reactions of the chorioepithelioma from the standpoint of diagnosis and prognosis, but on the other hand, in one of my cases and in the one Scott presented, curettage gave no evidence of diagnostic value, in fact was quite misleading. The biologic reaction may be of great diagnostic help when properly correlated with the clinical findings. Furthermore, I believe that the same biologic reactions may be of considerable prognostic value, judging from the way the reaction subsides after the tumors have been removed.

To our surprise, routine examination ten days post-operative revealed the presence of a black, soft nodule in the anterior vaginal wall. Following the discovery of this nodule, the Friedman test was found to be strongly positive. Chest plates were repeated but were still normal. A biopsy showed this nodule to be metastatic chorioepithelioma. Roentgen ray therapy was instituted. Forty-one days post-operative the chest plate first revealed an ovoid density suggestive of a newgrowth, and within a short time this process was diffuse throughout both lungs. A productive cough with blood-streaked sputum appeared. Soon afterward another interesting train of symptoms developed, that of difficulty in vision, projectile vomiting, severe headaches, and coma at intervals. A Friedman test of the spinal fluid was positive. She died on August 4, 101 days after her operation, or 146 days post partum.

This case reveals the high degree of malignancy of certain chorioepitheliomas and the wide distribution of their metastatic lesions. It also demonstrates the value of the Friedman test as an aid in the diagnosis and prognosis of this interesting neoplasm. It is interesting to speculate as to whether this chorionic carcinoma was present at the time of delivery.

DR. OTTO H. SCHWARZ, ST. LOUIS, MO.—About five years ago we had an experience with a tumor of this kind. Tissue from this patient, who had been eight weeks pregnant, showed histologic evidence of epithelial proliferation in a very few of the villi. She developed pain in the right lower quadrant and a month later a mass was found. When we operated, we found a mass coming from the upper portion of the uterus at its junction with the tube. This mass had deeply invaded the broad ligament in its posterior portion and could not be entirely removed, but there was nothing in the uterus itself. We found the tumor had its origin in the outer portion of the tube. On histologic examination one would also have had to make a diagnosis of chorioepithelioma, but the patient has now been well for a period of five years. No x-ray was given.

Regarding the Aschheim-Zondek test, it is interesting that one patient presented a rapidly growing uterus and a hydatidiform mole was suspected. The Aschheim-Zondek test was positive, and the surgeon insisted on emptying the uterus. To his surprise and amazement he delivered the patient of three small fetuses.

DR. WILLIAM A. SCOTT, TORONTO, CANADA.—Three previous speakers have shown that a hydatidiform mole may be present in the uterus and curettage not reveal its presence. I wish to record two cases in which this was true.

In the first case, the Aschheim-Zondek test was still positive three weeks after the removal of a mole, but a second curettage revealed no evidence of a chorioepithelioma. Beginning six months later there was slight spotting on three occasions. A second curettage was done, again with negative results, but the Aschheim-Zondek test was still positive. A total hysterectomy was then performed and a chorioepithelioma discovered, embedded in the wall, covered over with a thin layer of muscle as well as by endometrium. The slide showed two definite vesicles, but the histologic picture was a typical choriocarcinoma.

The second patient passed a mole four years ago, and then remained perfectly well until two months ago when she developed a small nodule in the skin on the back. This, on removal, proved to be a choriocarcinoma. Following this she had a slight amount of vaginal bleeding and was curetted, but no evidence of malignancy was found in the curettings. An Aschheim-Zondek test was positive in a dilution of 1:500, but the x-ray of the lungs was negative and no clinical evidences of other metastases were to be found. Therefore, a hysterectomy was done and the tumor was found again embedded deep in the uterine wall and covered with both muscle tissue and endometrium.

DR. WILLIAM P. HEALY, NEW YORK, N. Y.—We are inclined to agree with Wilson's histologic grouping of cases. I have had ten such cases, and they are always extremely malignant and almost always fatal. The two choriadenoma destruens patients are both alive.

## DESCRIPTION OF SPECIMENS

The specimens described here in detail were chosen because they demonstrate most clearly the complete phenomena of uterine bleeding and slough.

CASE 1.—Mrs. H. G. (No. 14 in our series), aged 29 years, entered the hospital May 31, 1938. Her menses occurred regularly every twenty-eight days with a three- to five-day flow. The last normal menstrual period began April 3, 1938. On May 8, 1938, spotting began and continued through May 28, 1938. On May 29 and 30, the two days prior to operation, there was no bleeding. Cramping pain persisted from May 8 to the time of operation. At operation, May 31, 1938, the uterus was removed supracervically with the unruptured left tubal pregnancy:

The uterus after supracervical removal is 7.5 by 5.0 by 4.0 cm. Its surfaces are smooth and glistening. On surfaces made by cutting, the decidua is 7 to 8 mm. thick. The myometrium appears normal.

The left tube is 9 cm. long, and in its greatest dimension in the midportion is 4.5 cm. wide. The lumen is filled with clotted blood. In the dilated central portion there is a placental site of a tubal pregnancy.

The uterine cavity contains no blood. The decidua is in folds which are as thick as 6.8 mm. after fixation in formalin. The decidua is covered with surface epithelium. The decidua is differentiated into compact, spongy, and basal zones identical in arrangement to that in *vera* of normal intrauterine pregnancy. The compact zone is as thick as 4 mm. (Fig. 1). The stromal cells are differentiated into typical decidual cells of pregnancy. There is a small amount of intercellular edema fluid. The gland necks are far apart, elongated, and narrow. The gland cells are flattened. Large blood filled venous sinuses are located in the compact zone. Spiral arteries and their branches reach to the surface. The spongy zone (2 mm. thick) contains considerable edema (Fig. 1). The glands which comprise most of the spongy zone are the typical Opitz glands of pregnancy. The cells are columnar. Some glands contain secretion. The stromal cells are small. Traversing the spongy zone are numerous venous spaces and spiral arteries. Around these latter structures the stroma is condensed. The basal zone is characterized by a dense stroma and glands that evidence less secretory activity than those located in the spongy zone. Some glands extend downward into the myometrium.

CASE 2.—Mrs. L. C. (No. 6 in our series), aged 30 years, para ii, entered the hospital Jan. 13, 1936. Her menses occurred every twenty-eight days, lasting four to five days. Uterine bleeding began on Dec. 1, 1935, and lasted four days. The patient considered this a normal menstrual period. On Dec. 11, 1935, she began to spot and have cramping pains, both of which continued until the time of operation on Jan. 14, 1936.

At operation the body of the uterus and the right tube containing the pregnancy were removed abdominally. The tube in its midportion was distended to a maximum diameter of 4 cm. The uterus, 7 by 5 by 4 cm., was soft and congested. The tissues were fixed immediately in aqueous-formol-chrome-sublimite. The decidua of this specimen is in folds, similar to those in Specimen 14. It is as thick as 4.3 mm. In Fig. 2 the decidua at either end is 2.9 mm. thick. The midportion is thin. It measures 0.8 mm. The thick portions have a surface that is thrown into papillary folds and projections. The tips of the papillary projections are edematous and similar to those in Fig. 1. The compact zone is narrow (0.9 mm.): The decidual cell formation is meager. The blood-filled venous sinuses are quite superficial. There are occasional small superficial regions of extravasation. The gland necks are short (0.0424 mm.) and have low columnar and cuboidal cells that evidence no secretory activity. The spongy zone is 2.0 mm. thick. The glands are tortuous and the cells are columnar and filled with secretion. The stroma is dense and the cells are small. The basal zone is thin and is similar to that noted in Fig. 1.

The thin midportion of decidua (0.8 mm.) has sharp borders of differentiation from the adjacent region. The surface is flat. The surface epithelium is intact. The compact zone is narrow in contrast to that of the thick regions. There is no edema. The decidual cells are few, small, and crowded closely together. The

# THE ARTERIAL PHENOMENA ASSOCIATED WITH UTERINE BLEEDING IN TUBAL PREGNANCY\*

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CLINICALLY, in instances of tubal pregnancy, uterine bleeding is one of the most constant symptoms and findings. Fitzgerald and Brewer (1935) in a study of 500 patients with ectopic pregnancy observed that bleeding of some character occurred in 82.4 per cent of these patients. The usual type of bleeding is characterized as a spotting or very moderate flow (71.2 per cent of patients, Fitzgerald and Brewer, 1935). The bleeding usually occurs intermittently or constantly for some time before operative procedures are instituted.

The bleeding has its origin in the uterine decidua in the vast majority of instances, and only rarely does it arise by blood flowing from the tubal lumen into the uterine cavity. The characteristic type of bleeding, spotting, has been explained upon the basis that the decidua desquamates much more slowly than in menstruation. Sampson (1914) and others have demonstrated that the bleeding is, as a rule, reflux flow from the venous spaces in the decidua.

The factors that bring about the bleeding are considered to be the death of the fetus and hormonal changes associated with such death. The complete anatomic and the physiologic phenomena in the decidua that produce desquamation and bleeding have not been fully described. It is with this phase that the present work is concerned.

## MATERIAL AND METHODS

In a series of more than 650 proved tubal pregnancies, it was necessary to remove the essentially normal uterine body in 16 instances. These uteri furnish the material for this study.† Traumatism of the uterus was avoided during abdominal hysterectomy by clamping the round ligaments. No instruments were applied to the uterus. There was no vaginal manipulation nor curettage of the decidua.

Each uterus after removal was opened and fixed either in 10 per cent neutral formalin or aqueous-formol-chrome-sublimate. The blocks of tissue taken were not larger than 10 by 5 by 3 mm. They all contained the entire thickness of the decidua and some myometrium. After embedding in paraffin, 7  $\mu$  sections were cut and arranged serially in each instance. The stains used were Mallory's connective tissue stain, hematoxylin and eosin, Bielschowsky-Maresch silver stain, and Best's carmine stain.

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Aided by the Albert B. Kuppenheimer Fund of St. Luke's Hospital, and a grant from Mrs. Emmons Blaine.

†Grateful acknowledgment is made to Dr. James E. Fitzgerald and Dr. George H. Gardner for a portion of these specimens.



The venous structures are moderately dilated and contain blood. The stromal cells are small.

CASE 3.—Mrs. E. D., aged 30 years, entered the hospital June 14, 1934. Vaginal bleeding, spotting to moderate, began April 1, 1934 and continued up to the time of operation. Her last menstrual period was from Feb. 15 to Feb. 19, 1934. Associated with the vaginal bleeding there was a soreness in the right lower quadrant. A diagnosis of right tubal pregnancy was made and on June 16, 1934, the uterus, both tubes, and the right ovary were removed for a tubal pregnancy and residues of pelvic infection.



Fig. 3.—Subepithelial hematoma of Gebhard. The intact decidua is approximately one-half as thick here as in the remainder of this specimen. (Spec. 6.)



Fig. 4.—Region evidencing early desquamation is shown to be strictly localized. The arrow indicates a terminal portion of a spiral artery that has been sequestered with a portion of decidua. This is shown at greater magnification in Fig. 21. The thicker intact portions of decidua have undergone partial involution as evidenced by the character of the glands.

Fibrous adhesions cover the uterus, both tubes, and the right ovary. The fundic portion of the uterus is 6 by 8 by 5 cm. The myometrium is 3.2 cm. thick. The right Fallopian tube has in its middle portion a circumference of 3 cm. It is filled with clotted blood. Adherent to the tube and the posterior surface of the uterus is a mass of clotted blood 10 by 9 by 2 cm. The decidua and a portion of the myometrium were fixed immediately in aqueous-formal-chrome-sublimate solution.

The cavity of the uterus studied under the dissecting microscope after fixation is lined with decidua that is arranged in folds and rugae similar to that found in

spiral arteries extend to the surface. The superficial capillary network is present. There is a slight extravasation of blood. Infiltration of leucocytes and lymphocytes is only occasional. The venous sinuses are not prominent. The gland necks are short and the cells are secretory in character. This is in direct contrast to the typical elongated gland necks with nonsecretory epithelium in the thicker regions of this specimen. The glands have extremely wide mouths. Some are as wide as 0.276 mm. In the adjacent thick portions the necks are 0.0424 mm. wide. In the spongy zone the glands are close together with only strands of stroma between them. The glands are wide in comparison to the glands in the thick regions. The glands in the former region are 0.339 mm. wide, while in the latter regions they are 0.127 mm. None of the cells of the glands in the thinned-out portion is as actively secreting as those in the thick regions. In this rather ill-defined spongy zone the venous structures are thinned and are not prominent. There is no edema. A basal zone cannot be differentiated.



Fig. 1.



Fig. 2.

Fig. 1.—Typical decidual reaction in the uterus in association with a seven weeks' tubal pregnancy. (Spec. 14.)

Fig. 2.—Midportion of the intact decidua is thin and compressed. At either end the intact decidua is thick and polypoid. (Spec. 6.)

In Fig. 3 the decidua is but 1.9 mm. thick. It is, therefore, thinner than many other regions in this uterus. It is not as thin as the low region described above (compare with Fig. 2). The zona compacta is markedly thinned. It contains little edema. The stroma cells are small and flattened and do not resemble true decidual cells. The gland necks are short and broad. In some regions there are small groups of leucocytes and lymphocytes just beneath the surface epithelium. A subepithelial hematoma of Gebhard is shown. The surface epithelium is stretched and flattened over this hematoma which is approximately 1.3 mm. in diameter. Venous sinuses are few and small.

The glands in the spongy zone show compression to a slight degree. They are secretory in character and resemble glands of pregnancy. There is some edema.

In the microscopic sections the thicker portions of the decidua are imperfectly arranged into compact, spongy, and basal zones. The surface epithelium is intact (Figs. 5 and 6). The superficial zone which represents the compact zone is edematous and contains numerous large venous sinuses. Many of the venous spaces are filled with blood. There is no extravasation and little evidence of diapedesis. There are only a few lymphocytes and plasma cells scattered through the stroma. Spiral arteries course through the spongy zone with occasional branching to reach to the surface epithelium. A superficial capillary network is present at the termination of the spiral arteries and their branches. The gland necks are narrow and they

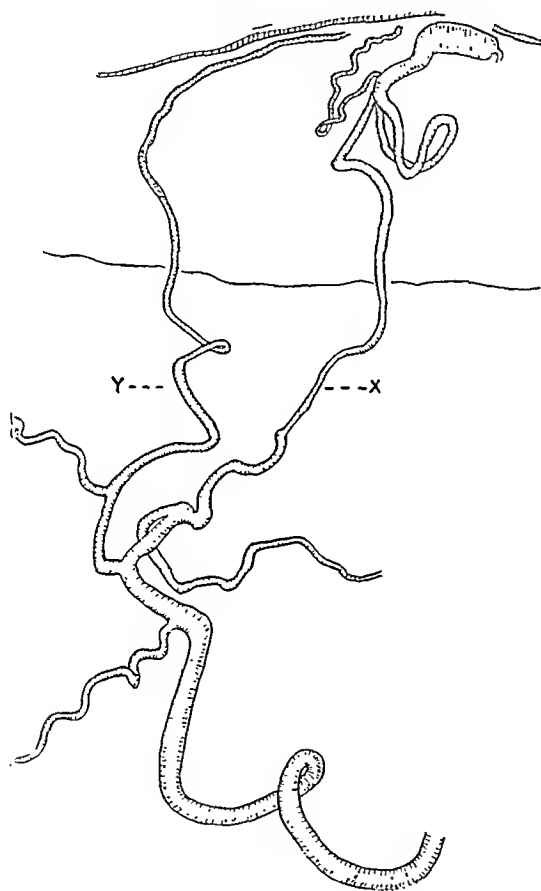


Fig. 7.—A three dimensional reconstructed model of the spiral artery supplying the portion of the decidua that evidences involution in Fig. 6. The myometrial-decidual junction and the surface epithelium are indicated. Branch (Y) is constricted through most of its course. Superficially it lies immediately subjacent to and parallel with the surface epithelium (see Fig. 13). Branch (X) is constricted basally and markedly dilated immediately beneath the surface (see Fig. 8). The constriction of branch (Y) is shown in Fig. 11 and that in branch (X) in Fig. 8. The surface epithelium is degenerated at the terminal portion of branch (X). These arteries represent true end arteries.

are shorter than those present in the decidua of a normal uterine pregnancy. The gland cells of the necks are large and cuboidal in contrast to the stretched-out epithelium which O'Leary (1929) described in early decidua vera. The stromal cells in the compacta are small, elongated, and have flattened nuclei. They do not resemble decidual cells.

In the poorly differentiated spongy zone there is moderate edema. The glands are infrequent. They are only slightly tortuous in shape. There is little secretion in their lumens. Glycogen is not stained in the gland cells after aqueous-formol-chrome-sublimite fixation. The glands do not resemble the glands of pregnancy. In this zone there are numerous large, blood-filled venous spaces. Many extend in

early pregnancy. The thick portions, which are 2.5 mm. thick, comprise 85 per cent of the total decidua (Fig. 4). The small isolated regions of low decidua (15 per cent) are 0.5 mm. thick (Fig. 5). Some of these thin regions have irregular, roughened surfaces to which blood clots, not exceeding 0.5 by 0.5 cm., are adherent (Fig. 4). Other thin regions have smooth regular surfaces (Fig. 5).



Fig. 5.—The decidua at the right is thick and edematous. At the left it is approximately one-half as thick and there is little edema. The surface epithelium is intact. A spiral artery of large caliber lies immediately beneath and parallel to the surface epithelium. This denotes the effects of compression, principally from the loss of edema in the involution phase before slough. Arterial spasm is noted in this vessel. (Spec. 3.)

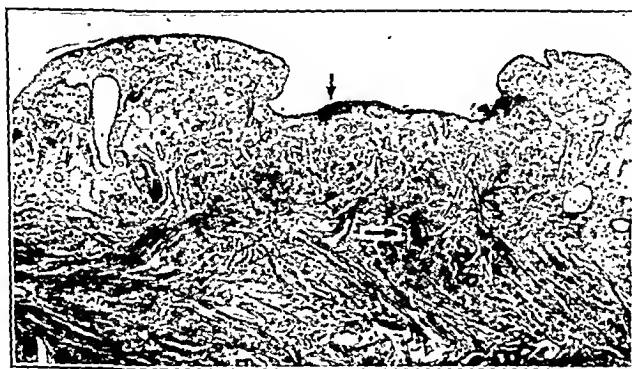


Fig. 6.—The decidual tissue at each end of this photomicrograph is thick, contains edema and large venous sinuses. Regression in the glands has occurred. The processes of involution have reduced the decidua by 50 per cent in the midportion. The surface epithelium is intact. No slough has occurred. The spiral artery that supplies this localized region is indicated by an arrow. The second arrow indicates superficial extravasation. (Spec. 3.)



Fig. 8.—Showing the entire thickness of the decldua and a portion of the myometrium. Branch (X) of the artery shown in Fig. 7 is dilated superficially and constricted in the myometrium (arrow). Extravasation and necrosis are present at the tip of the artery (see Figs. 9 and 10).



Fig. 9.—The tip of branch (X) shown in Figs. 7 and 8 has a defect in its wall with resulting extravasation by rhexis. The superficial epithelium is partially necrosed.

a vertical plane. The sinuses are most numerous and largest near the junction of the peripheral one-third and proximal two-thirds of the decidua.

The basal zone is differentiated only by the horizontal position of some of the glands and the fact that there is slightly less edema as compared to the spongy zone. The glands extend down into the myometrium for a short distance. All of these findings are shown best in Fig. 4. Large dilated venous sinuses in the myometrium are frequent (Fig. 4).

The thin portion of the decidua is in marked contrast to the thick region as shown in Fig. 5. The essential features that differentiate the two are the variations in amount of edema fluid and number and size of engorged venous sinuses. The borders of separation of the two regions are definite.

In the thin region (0.5 mm.) there is no separation of the decidua into zones such as described for pregnancy. The surface epithelium is intact. Throughout the decidua the stromal cells are elongated and small. They are equal in size and are packed closely together. They do not resemble decidual cells. There is no intercellular edema fluid. The glands are few in number, widely separated, and resemble those of a postmenstrual stage. They evidence no secretory activity. A spiral artery of large caliber reaches to the surface epithelium. Its course through the decidua is diagonal. Just beneath the surface it is bent laterally to lie parallel with the surface. The large loops just beneath the surface epithelium are dilated and contain little blood (Fig. 5). In this superficial region there is branching. There is a very meager capillary system at the terminal ends of this artery and its branches. In the myometrium just beneath the decidua, there is a constriction which, although not complete, is definite. The surface epithelium immediately over this large vessel is flattened in places. Some of the cells cannot be differentiated from adjacent stromal cells except by position and continuity with surface epithelium. Some cells evidence slight degenerative changes.

Fig. 6 is a photomicrograph of a section from a block of tissue taken from another portion of the same uterus, showing two thick regions (2.03 mm.) separated by a thin region (0.34 mm.). The localized thin region has a width of 2.9 mm. The thick regions are identical to those shown in Figs. 4 and 5.

The thin region, which is extremely low, has an intact surface epithelium (Fig. 6). This epithelium is flattened in numerous places. The flat epithelium is differentiated from the underlying stroma only by position and by continuity with adjoining surface epithelium. Occasional large surface epithelial cells, two to four times the usual size, are noted. The nuclei are large, irregular, and are stained poorly. Flat epithelial cells project over the edge of the cuboidal surface epithelium in places. The impression is obtained that this flattened epithelium is in the process of migrating over the surface. Many epithelial cells have irregular cell membranes and pyknotic nuclei. In this extremely low region of the decidua there is no differentiation into zones characteristic of pregnancy. In the superficial zone there are some regions of extravasation beneath the surface epithelium (Fig. 6, see arrow). These are located about the terminal ends of spiral arteries.

The stromal cells are compact, small, and spindle shaped. There is little edema. The glands are few, far apart, and resting stage in character. The cells in the gland necks are undergoing mitotic division. There are a few small venous spaces present. Scattered through the stroma are many leucocytes and lymphocytes.

The spiral artery located in the center of this involuted region (Fig. 6) is shown in a three dimensional reconstruction in Fig. 7. It approaches the decidua in a perpendicular fashion and divides into two main branches just before entering that structure. The larger branch (X) is but moderately coiled. It is constricted through most of its course through the decidua, and its lumen is empty. It branches once in the peripheral one-third of the decidua. The terminal portion of the arteriole is markedly dilated and is filled with blood (Figs. 7 and 8). Here extravasation is greatest (Fig. 8). The surface epithelium overlying this region is denuded and there is some small hemorrhage into the uterine cavity. Fig. 9 shows a portion of the tip of this branch, dilated and filled with blood. The endothelial wall is ruptured at one point and extravasation has occurred. In this region there are occasional capillaries found. In Fig. 10 extravasation about the tip of an unruptured terminal arteriole is shown. The surface epithelium is intact.

Figs. 4 and 14 are photomicrographs of sections from blocks of tissue that were taken from different portions of the same uterus. At either end of the sections the decidua averages 2.5 mm. while the low region is as thin as 0.5 mm. There is sharp differentiation between these regions. The thick portions are similar to the thick regions shown in Figs. 4 and 5. The glands evidence some slight secretory activity. The venous sinuses are numerous and contain blood.

The thin region of decidua has no intact surface epithelium except at the margins (Figs. 4 and 14). Where the covering epithelium is wanting, the decidual surface is very irregular. Glands, vessels, and stromal cells jut unevenly into the uterine

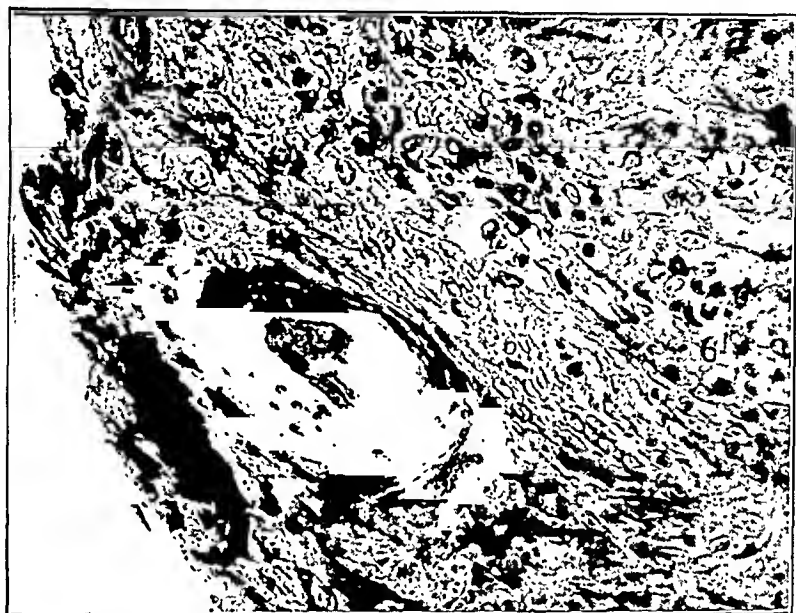


Fig. 12.—Extravasation and partial necrosis of the surface epithelium at the termination of the arterial branch (Y) (Fig. 7).

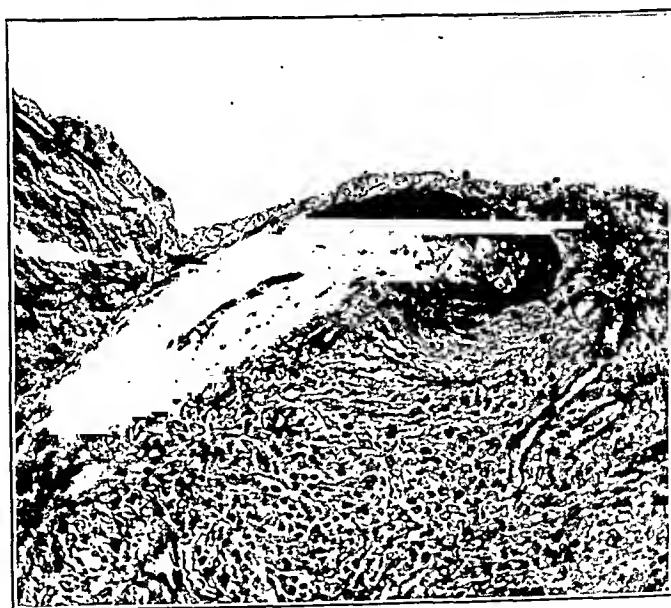


Fig. 13.—Intact surface epithelium overlying the horizontally placed large arterial branch (Y) near its termination (see Fig. 7).



Branch (Y) is relatively straight and uncoiled. It is constricted and empty (Figs. 7 and 11). It reaches to the surface unbranched. The surface epithelium is undergoing degenerative changes in the region where the artery terminates. The stroma is disrupted. The arteriolar wall is unruptured and extravasation has occurred (Fig. 12). A few blood cells have entered the uterine cavity. Near the tip of this branch the artery has a thick muscle coat, lies parallel to and immediately beneath the intact epithelium (Figs. 7 and 13).

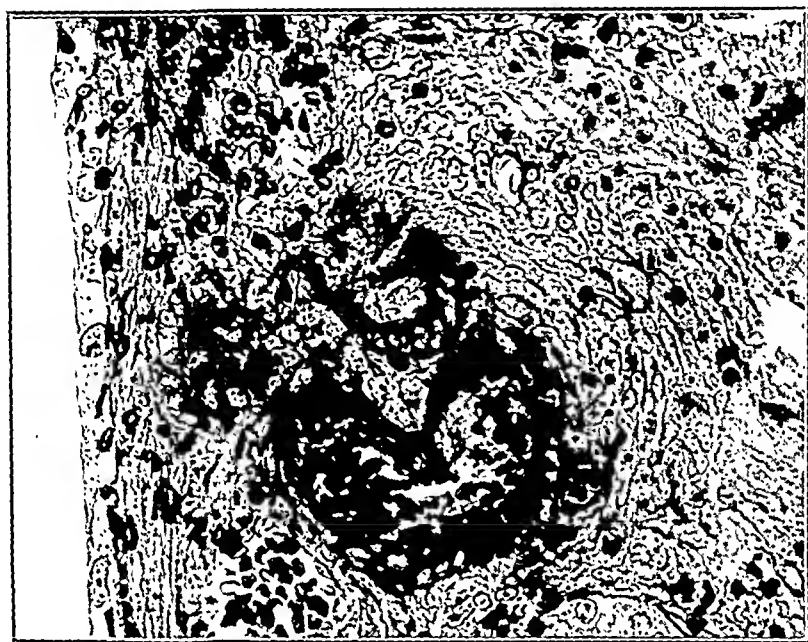


Fig. 10.—Tip of branch (X) (Fig. 7) with extravasation by diapedesis immediately beneath the intact surface epithelium.



Fig. 11.—Cross sections of a loop of branch (Y) (Fig. 7) demonstrating marked constriction near the myometrial-decidual junction.



as in the marginal regions where the surface epithelium is intact. This clearly demonstrates that as yet there has been little actual loss of tissue. These facts indicate this to be an instance of beginning desquamation. In the peripheral part of the decidua numerous small masses or flakes of "clastoidin" are found. They are located close to the vascular structures.

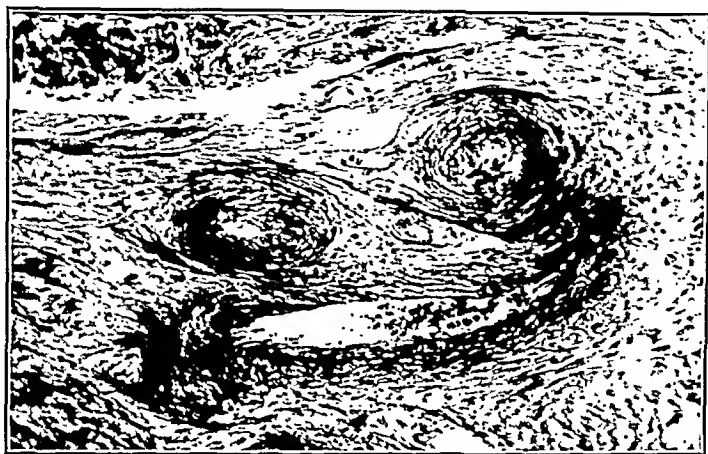


Fig. 16.—Cross and longitudinal sections of a spiral artery loop in branch (A) demonstrates constriction. The location of this constricted portion is indicated by an arrow in Fig. 14.



Fig. 17.—The terminal portion of a branch of the endometrial artery branch (A) (see Fig. 15) with its dilated lumen filled with fibrin.

The artery that is located in the center of the sloughing region in Fig. 14 projects toward the decidua in a perpendicular plane. Just before entering the decidua the vessel divides into two main branches (Fig. 15). Each enters the decidua in a slightly oblique manner. The larger branch (A in Fig. 15) is constricted over a short distance in the myometrium just beneath the decidua (Fig. 16). It has few coils in the proximal one-half of the decidua (Fig. 15). In the peripheral half, however, the coils are numerous and tight. Throughout the decidua this branch has little blood in its lumen. The artery divides into three branches in the peripheral decidua. Each branch extends to the irregular desquamating surface.

cavity. Blood cells, fragments of tissue, individual endometrial stromal cells, some surface epithelium, and precipitated fluid are located free in the uterine cavity just above these surfaces (Fig. 4). Many of the cells appear normal while others are definitely degenerated. In this region the thickness of the decidua is the same

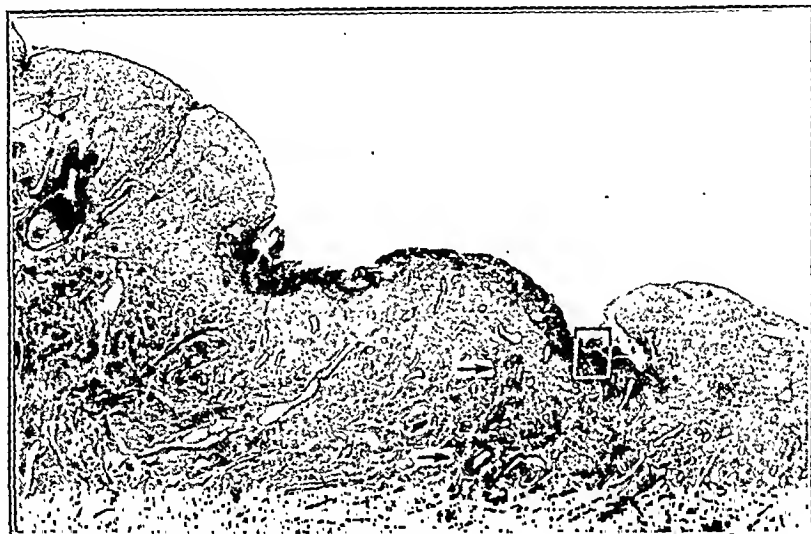


Fig. 14.—Characteristic localized region of superficial desquamation. The large artery that alone supplies this region is indicated by arrows. Extravasation is marked. (Spec. 3.)

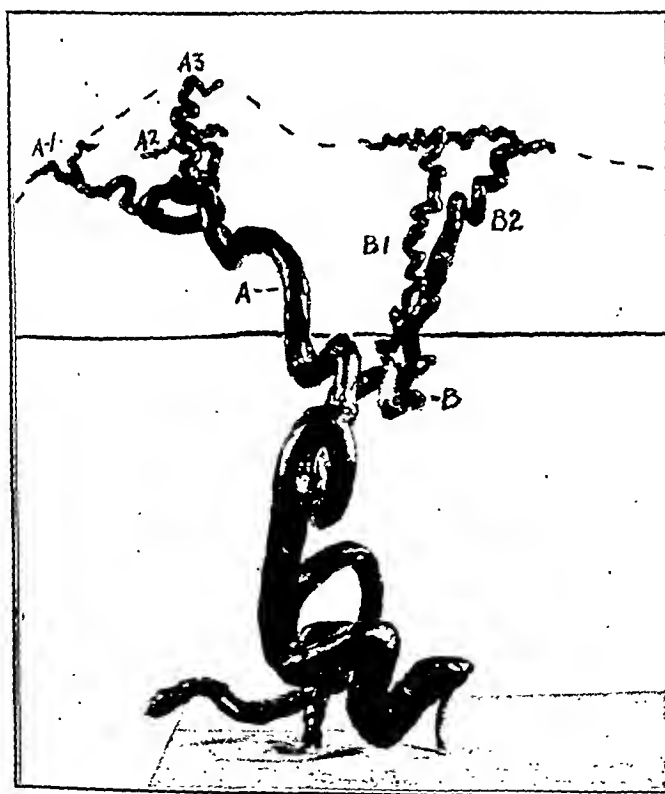


Fig. 15.—A three dimensional model of the end artery shown in Fig. 14 reconstructed from serial microscopic sections. The myometrial-decidual junction and the surface of the decidua are indicated. Each of the two main endometrial branches evidences physiologic constriction (see Figs. 16 and 19).

The endothelial cells have irregular cell membranes and the nuclei in many instances are pyknotic. There is no demonstrable capillary network here.

Fig. 18 shows the tip of branch (A, 2) (Fig. 15). The slightly dilated terminal arteriole has a defect in its wall at one point. The adjacent endothelium is undergoing degenerative changes. Through this defect extravasation has occurred. Blood fills the disintegrating decidual tissues and some is located in the uterine cavity. There is no capillary network.



Fig. 20.—Superficial half of a region of decidua, part of which on the left is desquamated, and part on the right that is still covered with surface epithelium. The blocked zone in Fig. 14 indicates this region. A spiral arterial branch with an empty lumen extends laterally beneath the intact surface epithelium. This is indicated by arrows.



Fig. 21.—Terminal portion of an artery (branch [B], Fig. 15) sequestered with a portion of decidua (see Fig. 4). There is no blood in its patent lumen and there is no hemorrhage about its tip. The constriction in this vessel is shown in Fig. 19.

About the terminal ends of each, extravasation has occurred. Fig. 17 shows the tip of branch (A, 1). It is slightly dilated and is filled with blood. It is located in a fragment of desquamating decidual tissue where it is occluded. There is considerable blood in the uterine cavity and in the disrupted stroma in this region.

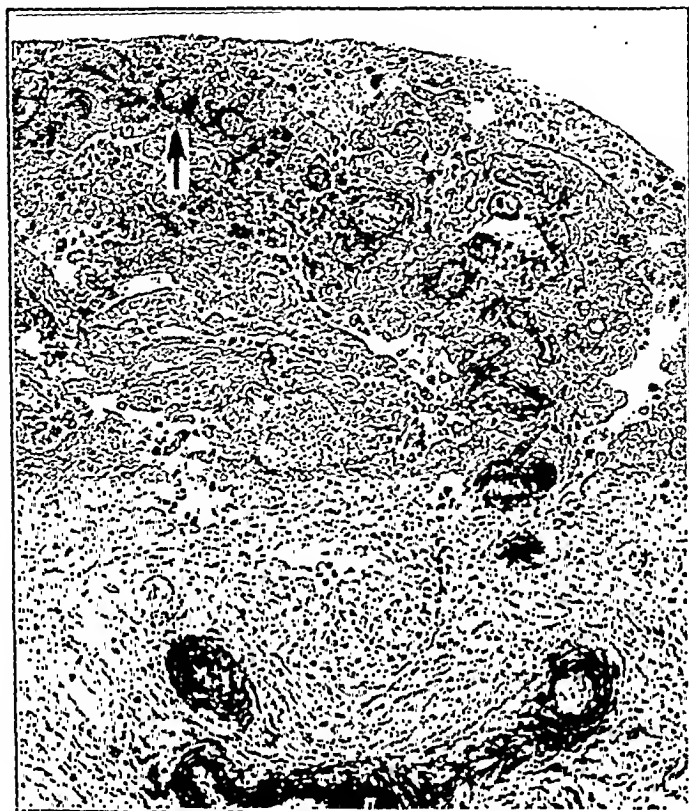


Fig. 18.—Superficial decidual tissues showing extravasation, disintegration, and slough. The artery supplying this region has a defect in the wall near its termination, through which extravasation by rhexis has occurred (arrow). The constriction in this artery that produced the ischemic necrosis and the resulting break in the arterial wall is shown in Fig. 16. (Spec. 3.)

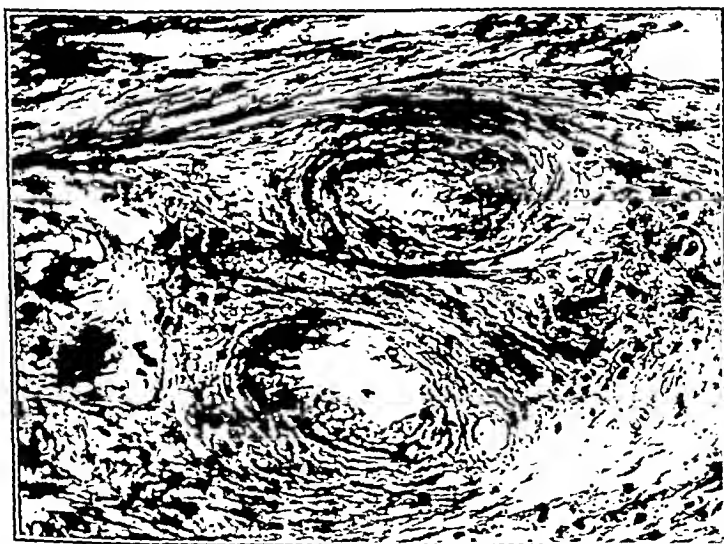


Fig. 19.—The loop of the spiral artery (branch [B], Fig. 15) evidences constriction.

This branch is constricted through most of its course and contains little blood. It bends laterally just beneath the surface (Fig. 20). Here the surface epithelium is intact. The branch is everywhere intact and its lumen patent. No capillary network is present.

The larger branch (*B*, 2) is tightly coiled. Near the surface it divides into several smaller branches. One branch is in the process of being desquamated with a bit of decidual tissue (Figs. 4 and 21). While extravasation is abundant here, there is no marked hemorrhage although the lumen is patent. One terminal branch lies parallel to the sloughing surface. Portions of the vessel are involved in the desquamation, its lumen is patent, yet no hemorrhage is evident. No capillary network is present.

In another block of tissue from the same uterus the findings are similar to those described above. The thicker portion of the decidua is 1.4 mm. thick. It is covered with surface epithelium. The decidua is not divisible into layers or zones. There is little edema in any region. The stroma cells are homogeneously distributed. They are spindle shaped and do not resemble decidual cells. The venous sinuses are not as large or as numerous as in other blocks of tissue described above. Spiral arteries reach to the surface. The glands are few, far apart, and are only moderately active in secretory character.

The thin portion has a maximum thickness of 0.9 mm. This portion resembles in all details that shown in Figs. 4 and 14. In Fig. 22 a large artery is shown projecting free into the uterine cavity. Its lumen is patent. There is little blood in its lumen. There is no hemorrhage about its open end. Serial reconstructions demonstrate a localized constriction of its lumen near the myometrial-decidual junction (Fig. 23).

#### DISCUSSION

In instances of tubal pregnancy it is a well-known fact that the endometrium develops into typical decidua (Fig. 1). The extent of development depends upon a continued growth of the fetal trophoblast, uninterrupted corpus luteum stimulation, and continued pituitary hormonal secretion. Certain alterations in any one of these, each dependent upon the other, bring about regression of the decidua with associated uterine bleeding.

The first phase of the process of uterine bleeding is involution. In describing normal menstruation, Bartelmez (1931) stated that this phase had been neglected recently by most authors. He demonstrated (1931) that involution reduced the thickness of the endometrium by 50 to 60 per cent before slough and bleeding occurred. He showed (1933) that involution was brought about principally by four factors: (1) a disappearance of edema, (2) a loss of secretion from the glands, (3) a diminution of the blood supply, and (4) a diminution in size of the gland and stroma cells.

A distinct advantage in the study of involution in our material is had in the fact that in many instances one section properly chosen shows small regions of involution or slough bounded on all sides by decidua that has been less involved (Figs. 2, 4, 5, 6, and 14). These small isolated regions of involution and slough are comparable to similar localized regions in the endometrium in normal menstruation. Bartelmez (1933) stressed that menstruation in the human being may involve but small local regions at a time and that only gradually the entire mucosa becomes involved in the phenomenon.

The loss of edema fluid which usually occurs first in the process of involution is shown in Figs. 2 and 5. The decidua has been reduced in

The terminal portion of branch (*A*, 3) has extravasation about it. No capillary network is evident. The minute arteriolar branches, of which there are several, are not involved in the desquamation to the extent observed in branches (*A*, 1) and (*A*, 2). The tips of each are patent but no great hemorrhage has occurred.

Branch (*B*) (Fig. 15) is constricted also in the myometrium just beneath the decidua. The constriction is definite (Fig. 19). The vessel as it courses through the decidua contains little blood. At the myometrial-decidual junction a small branch is given off that extends to the surface (branch *B*, 1, Figs. 15 and 20).



Fig. 22.—The partially desquamated decidua with a portion of myometrium is shown. The spiral artery with its empty lumen juts free into the uterine cavity. There is no hemorrhage about its tip. The constriction in this artery is shown in Fig. 23.

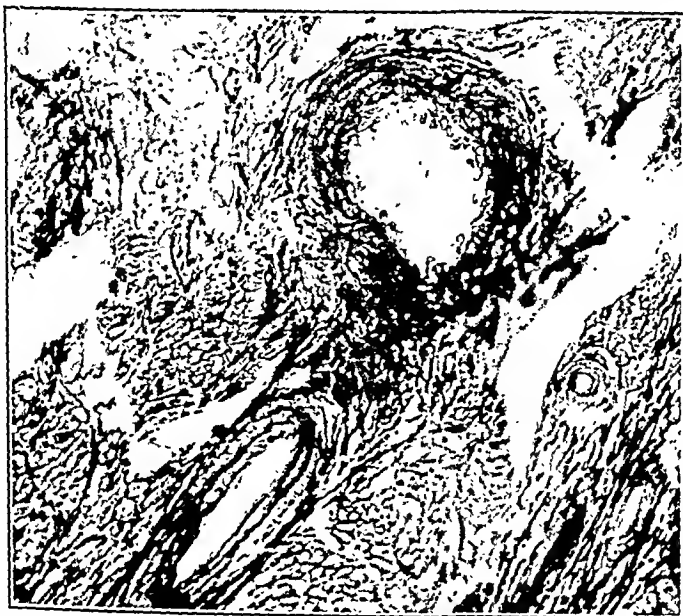


Fig. 23.—Physiologic constriction in the artery shown in Fig. 22.

stroma and by the fact that the decidua here is 1.9 mm. thick, whereas the regions that still retain edema are as thick as 3.8 mm. This is similar to normal menstruation in which Bartelmez (1933) states that loss of edema usually precedes extravasation and hematoma formation. Extravasation in the superficial portions of the decidua which evidence involution is a constant finding here (Figs. 6, 8, 9, 10, and 12) as it is in menstruation.

When involution has progressed further, pictures such as Fig. 4 are observed. In the midpoint the decidua is approximately 50 per cent as thick as the adjacent, surrounding less involved tissues. All the edema fluid has been lost. The glands have ceased their secretory activity and are typical of a resting stage. The gland and stroma cells are reduced in size. In addition there has been a reduction in circulation since the superficial capillary bed is absent. The terminal arterioles have in many places endothelial cells with pyknotic nuclei and some have defects in their walls. Through these defects blood escapes into the surrounding tissue (Figs. 9 and 18). Thus, about the terminal vessels extravasation is noted. In some instances (Fig. 10) the surface epithelium is intact over these vessels. In others, the surface epithelium is absent only over the terminal tip of the vessel (Figs. 8 and 12).

In conjunction with the reduced flow, disruption of the capillary bed, and extravasation, there is a necrosis of the surface epithelium in this specimen (Fig. 4). The necrosis in places has proceeded far enough so that the surface epithelium is destroyed. Involved in this is a degeneration of the stroma cells. A disruption of the stroma framework results from the reduced circulation, the distention of the extravasated blood, and the presence in the locality of leucocytes and lymphocytes. Bartelmez (1933) described this for menstruation. This whole phenomenon then results in a desquamation and disintegration of the superficial decidual structures. The tissue separates and is cast off in fragments and individual cells (Fig. 21) as Novak and TeLinde (1924) and Bartelmez (1931 and 1933) have described for menstruation. The slough involves the terminal ends of arterioles (Figs. 17, 18, 21, and 22), veins, stroma, surface epithelium, and glands.

In some instances the sloughing process occurs in such a way that arteries jut free into the uterine cavity (Figs. 21 and 22). Here there is no clot in the lumen and there is no hemorrhage about it. The absence of blood in these vessels, the absence of clots in the lumen, and the absence of hemorrhage about the tips suggest vascular control for these phenomena.

#### ARTERIAL SYSTEM

The study of the spiral arteries in the decidua of the specimens reported here shows that they are located every 4 to 8 square millimeters. A similar spacing of these vessels was noted in normal human menstruating uteri by Bartelmez (1933). The arteries branch in the superficial one-third of the decidua and terminate near the surface in capillary networks.

It has been demonstrated that each small localized region of decidua that is involved in early involution, disintegration, and slough in these specimens is that which is supplied by a single spiral artery and its branches (Figs. 5, 6, and 14).



thickness in a definitely localized region from 3.5 to 1.0 mm. as compared with the adjacent normal decidua in Fig. 2. The glands are markedly compressed. They are in a typical secretory phase and the cells are not decreased in size. The compact stroma is compressed without decrease in size of the individual cells. Compression of the glands is indicated first, by decreased length, second, by increased width in many instances so great that the glands are adjacent with little intervening stroma, third, by marked widening of the gland mouths, and fourth, by absence of gland necks. The spiral arteries that reach to the surface terminate in capillary networks. Slight extravasation has occurred. The venous spaces have disappeared. The leucocytic, lymphocytic and plasma cell infiltration, stated by Novak and TeLinde (1924) to occur prior to menstruation, is evident here. That these regions have been thicker and have become thinned is suggested by the above facts and in addition is proved by a study of the arteries. The arteries here are much larger in comparison to the thickness of the decidua (Fig. 5). The large caliber of the vessels immediately beneath the surface epithelium demonstrates that the decidua has become thinner. Thus, in this particular locality the beginning of involution is characterized primarily by a reduction in thickness of the decidua due to a loss of edema fluid.

In another specimen, however, involution has been initiated by a regression of the glands. They are not secretory in type but resemble a resting stage (Fig. 4, thicker portion of decidua). The cells are reduced in size and glycogen is not stained following aqueous-formol-chrome-sublimate fixation. That these glands were previously fully developed and secretory in character and have regressed is evidenced by the fact that all the other elements of the decidua denote complete corpus luteum stimulation. These are namely, the development of venous sinuses, spiral arteries reaching to the surface, a superficial capillary network, and marked edema. It does not seem probable that all these evidences of stimulation could be present without some associated stimulation of the glands. Here there has been little apparent loss of edema fluid and consequently little reduction in the thickness of the decidua. There is no extravasation, rhexis, or slough evident in this region. It is conceivable that even under normal conditions such as menstruation, involution may be heralded in by any one of the different features that characterize it. Bartelmez (1933) has indicated this to be true. This specimen also demonstrates small thin regions in which the glands have regressed as noted above and in addition there has been a loss of edema fluid which accounts for its thinness. That this is a regression phenomenon is conclusively demonstrated by the fact that large spiral artery loops reach to the surface (Figs. 4, 5, 8, and 13) in contrast to the normal position and caliber of such vessels.

The third factor in involution, extravasation and a diminution of the blood supply, is demonstrated in Fig. 3. A subepithelial hematoma of Gebhard which results from a rupture of the superficial capillary bed is shown. Similar hematoma formations are constant features of normal menstruation. Preceding this rupture and hematoma formation, there has been a loss of edema fluid as evidenced by the compactness of the



slough involves at first only the tissue lying immediately above the dilated terminal branch of an artery which is constricted throughout most of its course in the decidua (Figs. 7, 8, 11, and 12). The vessel wall is everywhere intact. In later stages of slough (Figs. 4, 14, 17, and 18) the loss of tissue is greater and extravasation is more marked. The artery that supplies this region evidences constriction near the myometrial-endometrial junction (Figs. 16 and 19). The ischemic necrosis that results from such constriction is indicated not only by the loss of tissue but also by a disruption of the endothelial wall in a terminal branch of this artery (Fig. 18). Thus, extravasation by rhexis is demonstrated.

In those thin regions in which slough is more extensive, the terminal branches of the arteries are involved in this process. Figs. 4 and 21 show a terminal portion of an arterial branch cast off into the uterine cavity in conjunction with decidual tissue. There is little extravasation and no hemorrhage about the open tip of this vessel. The patent and empty lumen indicates constriction and this phenomenon is shown in Fig. 19. Figs. 22 and 23 also demonstrate this phenomenon in its entirety. These phenomena indicate that during the phase of slough arterial structures are involved in the slough and that bleeding from these arteries is directly controlled by physiologic vascular constriction. In some instances in these specimens masses of fibrin fill the dilated terminal arterioles (Fig. 17). This may, in part, control the loss of blood.

We believe that the evidence presented indicates that arterial constriction accounts for the superficial extravasation, involution, disintegration, and slough that eventuate in uterine bleeding in tubal pregnancy in a manner identical to that demonstrated in menstruation by Bartelmez (1931 and 1933) and Markee (1933 and 1936). Furthermore, arterial hemorrhage during the phase of slough is probably controlled by physiologic vascular constriction.

### CONCLUSIONS

1. The external bleeding present in most instances of tubal pregnancy is uterine in origin and is essentially a reflux venous flow.

2. The bleeding is associated with involution and desquamation of the uterine decidua.

3. In the early phases, the portions of the decidua so involved are small and are limited to the tissues supplied by a single spiral artery and its branches.

4. These arteries are true end arteries.

5. Involution, which results from constriction in the spiral arteries, may reduce the thickness of the decidua by approximately 50 per cent before slough occurs.

6. Marked superficial extravasation and the diffuse infiltration of leucocytes and lymphocytes occur during the involution phase.

7. The necrosis and disintegration of the superficial decidual tissues results from the ischemia produced by physiologic vascular constriction.

8. The terminal portions of spiral arteries that are involved in the sequestration of the decidual tissues do not evidence any extensive hemorrhage as a consequence of the physiologic vascular constriction in these arteries.

9. The phenomena of involution, extravasation, superficial ischemic necrosis with disintegration and desquamation, the absence of arterial hemorrhage, and the demonstration of physiologic vascular constriction described here are similar to the findings in normal menstruation.

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This immediately indicates the importance of the spiral artery. There are many such localized regions scattered throughout the decidua. As these processes, typical of menstruation continue, the number of small localized regions increase, coalesce, and as a result, larger portions of the decidua become involved.

The importance of the spiral arteries in normal menstruation has been demonstrated by Bartelmez (1933), Markee (1933 and 1936), and Daron (1936). Bartelmez (1933) confirmed the suggestion that the processes of involution, disintegration, and slough were the result of ischemic necrosis. He demonstrated that ischemic necrosis resulted from physiologic vascular constriction. The vascular constriction frequently occurs in the spiral arteries in the myometrium just beneath the endometrium. Markee (1933 and 1936) in studying endometrial transplants in the anterior chamber of the eye in the macaque observed that individual arterial constriction might endure for as long as forty-eight hours. During this period the superficial portion of endometrium supplied by the particular artery in spasm became ischemic and appeared white. With relaxation of the spasm, the renewed circulation burst through the terminal capillary system and produced the superficial hematoma of Gebhard. As the time of menstruation approached, the periods of constriction greatly predominated over the periods of relaxation. Markee concluded that the reduced circulation accounted for the superficial necrosis of the endothelium, stroma, superficial epithelium and glands which eventuated in menstrual disintegration and slough. Daron (1936) demonstrated that the basal zone of the endometrium is supplied by an arterial system which is separate from the arterial system that supplies the remainder of the endometrium. These arteries, he showed, did not manifest the profound physiologic vascular constriction noted in the larger spiral arteries. In this manner he explained the absence of necrosis of the basal zone in menstruation.

In the specimens of this report, physiologic vascular constriction and the resulting phenomena are identical to those phenomena observed in normal menstruation as described above. That physiologic vascular constriction does occur is demonstrated in Figs. 7, 8, 11, 16, 19, 20, 21, 22, and 23. This phenomenon is found in the spiral arteries supplying the localized zones of involution, extravasation, and slough. Figs. 5, 6, and 14 show the relation of these vessels to their localized zones.

The results of such physiologic vascular constriction are, first, involution. The process of involution is usually initiated by the loss of edema fluid as noted above. Figs. 2, 5, and 6 show regions in which edema fluid has been lost without slough and with intact surface epithelium. The constrictions in the spiral arteries supplying these regions are shown in Figs. 5, 7, 8, and 11. The small localized regions of involvement in these specimens are supplied by a single spiral artery as noted above. That such an artery is an end artery is evidenced by the fact that constriction of the main vessel or large branch produces an ischemic necrosis of all the tissues supplied by this vessel or branch. Apparently any collateral circulation that may be present is not adequate to prevent necrosis of the tissues supplied by these end arteries.

In these thin regions undergoing involution extravasation is more marked than in the thicker adjacent region (Figs. 3, 6, 8, 9, 10, and 12.) It is in the thin, involuting region that vascular constriction is noted. The extravasation occurs at or near the terminal ends of the spiral arteries and their associated capillary networks (Figs. 6, 8, and 10). One artery of large caliber is shown in Fig. 13 to lie horizontally to and immediately beneath the intact surface epithelium, which indicates the compression resulting from thinning of the decidua in this region. In serial sections approximately 1 mm. distant, the terminal end of this artery is found. It lies near the surface, and about it there is marked extravasation. The surface epithelium immediately overlying it, and here only, is partially disrupted. The constriction in this particular vessel is shown in Fig. 11. Fig. 5 also demonstrates in another portion of the same uterus arterial compression and lateral deviation associated with involution prior to slough. Constriction is noted in this vessel also.

Continued vascular constriction results in disintegration and slough of the superficial decidual tissues in regions of involution as described above. Fig. 8 demonstrates the earliest phase of slough observed in the specimens reported here. The

We have always taught that if one suspects an ectopic pregnancy, and a curettage is done and the endometrium is found to look pretty definitely like early decidua, without chorionic villi, one can be sure that an extrauterine pregnancy exists. Perhaps we should modify our concept somewhat. I now have three cases in which the endometrium looked quite typical of early pregnancy, there being very definite deciduallike change in the endometrium without chorionic villi, and no tubal pregnancy existed. In fact, one girl had had a previous bilateral salpingectomy. In one case in which the Friedman test was positive only a corpus luteum cyst was found at operation. Apparently, then, there is some variation in the response of the endometrium to the progesterone or possibly, as is suggested by Browne's pregnandiol determinations, some variation in the amount of progesterone which is produced in pregnancy, whether intra- or extrauterine.

Just as there is a variation in the endometrial build-up, so is there a variation in the method of casting off the early decidua. The way described by Jones is undoubtedly the usual one but just as we occasionally see membranous dysmenorrhea we see, now and then, an entire endometrial cast come away from the uterus. The sequence of events is: Tubal rupture, death of the fetus, degeneration of the corpus luteum, withdrawal of progesterone, and finally shedding of the decidua.

Now my last point: Is the endometrium the only source of vaginal bleeding in tubal pregnancy? Jones said he thought the endometrial bleeding was the usual cause but I think I have one case which definitely proves it is not the only method. In order to have it we must assume death of the fetus and shedding of the endometrium. Some time ago I operated upon a ruptured tubal pregnancy of four months' duration in which there was vaginal bleeding. The fetus was definitely alive and I believe the bleeding must have come through the tube and through the uterus into the vagina, and not from the endometrium.

DR. J. C. LITZENBERG, MINNEAPOLIS, MINN.—As you will remember, the older writers on this subject thought that the bleeding came from the site of the implantation of the ovum in the tube. Sampson has proved that the bleeding from an ectopic pregnancy was chiefly from the uterus and not from the tubes.

In 1920 I confirmed the findings of Sampson with further evidence. There was no blood in most specimens of tubes except for a very few millimeters, between the implantation of the tube and the uterus. I was unable to find any evidence of blood coming from the site of the implantation. In a case of interstitial pregnancy studied by serial section and reported before this Society, there was no blood coming from the implantation site, and absolutely no blood in the tubes toward the uterus. Jones has gone several steps farther and has told us just where the blood comes from, and why.

DR. GEORGE W. CORNER, ROCHESTER, N. Y.—It is most interesting to see that bleeding from the uterus in tubal pregnancy in its anatomic features closely resembles that of normal menstruation. This fact can be correlated very plausibly with the hormone-deprivation hypothesis of menstruation, discussed in my address of yesterday, because (as we may suppose) while the implanting ovum is struggling for a hold in the unfavorable environment of the Fallopian tube, the output of gonadotropic substance from the chorion is inadequate or inconstant and the production of ovarian hormones is disturbed. The uterine bleeding of ectopic pregnancy may well, therefore, be hormone-deprivation bleeding.

The conjecture of Schwarz that the direct cause of the bleeding is contraction of the uterine muscle is difficult to reconcile with experiments of Markee, in which estrin-deprivation bleeding occurred in endometrial grafts in the anterior chamber of the eye. In these grafts little or no uterine muscle is present. The vascular disturbance must therefore be located in the endometrial arteries.

I am glad that Schwarz has suggested trial of progesterone in the pre-eclamptic state. No one would be happier than I if progesterone were found to cure any one, of any disease. An experiment of this sort, interpreted as encouraging, was made in Edinburgh and reported about two years ago by Dr. Suzanne Paterson. Others who try this therapy should use large doses of progesterone.

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## DISCUSSION

DR. OTTO H. SCHWARZ, ST. LOUIS, MO.—The work of Jones and his associates shows beyond question that the changes that occur in the endometrium in the cases of uterine bleeding of extrauterine pregnancy are similar to those occurring in the endometrium at the onset of normal menstruation. Clinically we have always regarded the onset of continued uterine bleeding in extrauterine pregnancy as a sign of the disturbance of the pregnancy.

The most striking change that has been demonstrated by Jones takes place in the spiral arteries which, in my opinion, are entirely similar to those occurring in the normal endometrium at the onset of menstruation, as described by Bartelmez, Markee, and others, which the author has referred to. The underlying change preceding menstruation, irrespective of the causes, is the constriction of the spiral arteries. What causes them to constrict? I feel most likely that in the normal cycle it is the diminution of progesterone.

We all know theelin has a stimulating effect on smooth muscles and that progesterone has a relaxing effect. In pregnancy I believe that this relaxing effect has much to do with increasing the caliber of the uterine vessels, especially in the early months. This thought has led me to suggest that in cases of clear-cut pre-eclampsia the hypertension arising gradually may be caused by the withdrawal of the progesterone. We know in these cases that there is a constriction of the arterial loop of the capillaries of the nail bed with dilatation of the venous loop. In case of pre-eclampsia and eclampsia, we have always looked for some pressor substance to explain this phenomenon. It is interesting to mention here that Corner yesterday stated that some pressor substances have also been looked for as the cause of the constriction of the spiral arteries in the phenomenon of menstruation, and also without avail. Could not the deprivation of progesterone be the most important factor? Low pregnandiol figures have been reported for pre-eclampsia and especially eclampsia. With these thoughts in mind we are going to use progesterone in clear-cut cases of pre-eclampsia.

DR. RICHARD W. TE LINDE, BALTIMORE, MD.—Jones has shown in a very clear fashion the similarity between the mechanism of bleeding from the endometrium of the decidua of an ectopic pregnancy and from the menstruating endometrium. The changes in the endometrium associated with early pregnancy, extra- or intra-uterine, and those in the late premenstrual period are subject to rather wide variations, wider, I believe, than are generally appreciated. It has always amused me to hear men speak of an eighteen-day endometrium and a twenty-one-day endometrium as though they could look through the microscope and tell from looking at the endometrium the exact day of the cycle. I do not believe that it can be done quite that accurately.

Some years ago I made a careful histologic study of the endometria of very early pregnancies and compared them with some late premenstrual endometria in which no pregnancy existed. In some cases, the endometria had more of the characteristic changes of early pregnancy in the late premenstrual nonpregnant cases than in some of the early pregnancies. For example, in the case of the Miller ovum obtained on the twenty-third day of the menstrual cycle, there was less glandular change, which we consider characteristic of pregnancy, than in some nonpregnant endometria at that same stage of the cycle and no deciduallike change in the stroma cells except in the proximity of the embedded ovum. This stroma change only near the ovum makes me wonder whether the chorionic tissue does not have some power to generate progesterone even at this early stage instead of taking over the function at the seventieth to ninetieth day, as suggested by Browne. I would like to know whether Corner has observed this in monkeys.

## THE OVARIAN HORMONES AND EXPERIMENTAL MENSTRUATION\*

GEORGE W. CORNER, M.D., ROCHESTER, N. Y.

*(From the Department of Anatomy, the University of Rochester, School  
of Medicine and Dentistry)*

OUR mastery of the ovarian hormones and knowledge of the physiology of menstruation have reached a point at which the menstrual cycle can be successfully imitated, in a castrate monkey or human female, with no other armament than a syringe and an ampoule of estrone. By merely timing, in a suitable manner, the course of estrone treatment to give a monthly cycle of estrone deprivation, a cycle of vaginal bleeding will occur, not externally distinguishable from natural menstruation. If any critical witness objects that this bleeding cannot be true menstruation, because the endometrium from which it proceeds has not undergone the so-called "premenstrual" changes, we may ask him to await the conclusion of this discourse before forming a judgment. Meanwhile we can satisfy his requirement by incorporating in our experiment suitably timed courses of progesterone, thus producing cyclically the premenstrual state and then in sequence the menstrual breakdown. Admittedly this refinement of the experiment is difficult to achieve in practice; effective balancing of the two hormones is critical and the histologic result not always perfect, but it will be agreed at least that we possess the means of producing, by the ovarian hormones alone, specimens exhibiting menstruation-like bleeding from the premenstrual endometrium. Having progressed thus far, the next step is to consider to what extent these experimental facts can be applied in explaining the natural cycle of the uterus.

When I began studies of menstruation in the Rhesus monkey, in 1920, it was soon apparent that very often the events of the cycle are similar to those of the human cycle as generally understood; that is, ovulation occurs about the middle of the interval between two menstrual periods; the corpus luteum is therefore present during the premenstrual phase (for which we now know it is responsible), and its retrogression is contemporaneous with the menstrual breakdown. On the other hand it turned out<sup>4, 5</sup> that in Rhesus there are often menstrual cycles without ovulation, therefore without the corpus luteum and consequently without premenstrual changes in the endometrium. In such cycles the bleeding occurs from an endometrium in the interval stage (compare Figs. 1 and 2).

Such a conclusion, already foreshadowed by the observations of Heape and Van Herwerden, has been amply confirmed, as regards the monkey,

\*Read, by invitation, at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

The amount of ovarian hormones acting upon the endometrium is the end result of a complicated set of chain reactions, especially under the disordered conditions of an ectopic implantation. Normal responses of the uterus in the cycle or in pregnancy require a very critical balance between the ovarian hormones. It seems no wonder that their effects are variable when they are disturbed.

DR. OTTO H. SCHWARZ, St. Louis, Mo.—The activities of the nail bed are similar to the capillaries. The capillaries shown by Jones possess smooth muscle, but, irrespective of that, the corpus luteum may act on the vessels. It would be well to supplement any progesterone treatment with a study of the capillaries.

DR. EMIL NOVAK, BALTIMORE, MD.—In this discussion there has been repeated reference to the analogy which exists between the endometrial desquamation of tubal pregnancy and that of normal menstruation. While this may be granted, one may properly compare it also with the casting off of the decidua at parturition. I mention this because the material presented by Jones is difficult to interpret unless one knows the status of the tubal gestation in the reported cases. Is the pregnancy still progressing, or has the embryo long since succumbed? In the latter case, for example, the menstrual cycle can again be resumed, so that the blood vessel changes are those of the cycle, and they cannot be considered characteristic of tubal pregnancy.

The fact that blood vessels open directly on the surface during menstruation has long been known, but the more characteristic changes, according to the work of Markee and others, involve the more deeply placed spiral arterioles, and we know little as yet concerning the histologic changes concerned and the nature of the endocrine control of these blood vessels. Important though involution may be in association with endometrial desquamation, I do not believe it is quite as constant as many believe. If we study the tissue thrown off at menstruation, we frequently find considerable masses which still show large scalloped glands and a stroma characterized by granular degeneration rather than involution. The same observation may be made in the study of the large uterine casts which are at times thrown off after the death of the embryo in cases of tubal gestation.

DR. HAROLD O. JONES (closing).—All the details obtainable, including the measurements and the clinical evidence as to the death of the fetus, together with all factors that we thought pertained to this subject, are given in the published work. Time would not permit bringing those details to your attention.

I think we missed some of Sampson's work when he demonstrated before this Society the inability to inject the vascular bed during menstruation. Recent studies now being carried on by Bartelmez show that he is unable to get perfect delineation of the spiral capillaries in the menstruating endometrium.

We know that the decidua in the uterus of tubal pregnancy does present a very unusual pattern, and we agree that the factors that control these variations have to do with the reactions in fetal death. We have no way of determining that definitely, but we have contributed in our published article all the information that we could possibly get on that problem.

are vascular in nature. Recently, direct observation of the menstruating endometrium under low powers of the microscope has been achieved by Markee, by the ingenious method of watching small grafts of endometrium growing in the anterior chamber of the eye. Such grafts behave as the same tissue did when at its original site; they bleed during menstruation and after deprivation of estrin. Markee's observations have been reported at scientific meetings and will appear shortly in the Carnegie Contributions to Embryology. He finds that natural menstruation in the grafts proceeds in a regular sequence, with first a phase of constriction of the coiled arterics. As each of these arteries contracts, the region it supplies is rendered ischemic for several hours. After this the artery relaxes, and the blood flow is resumed, but here and there the capillaries of the endometrium, weakened or damaged by the ischemia, rupture and set up temporary small local hemorrhages.



Fig. 3.—Menstruation from an early premenstrual endometrium, first day (Macaque C.19).

The confluence of these local hemorrhages constitutes the total menstrual breakdown. It is a significant fact that the vascular changes observed by Markee are alike whether or not the process is associated with ovulation. The only difference between standard ovulatory menstruation on one hand, and anovulatory menstruation or estrin-deprivation bleeding on the other, is that in the first case, and not in the second, the corpus luteum hormone has been present and has produced the so-called premenstrual changes. In the first case the uterus bleeds from a premenstrual endometrium; in the second case it bleeds from an interval endometrium. These facts are sufficient to show that ovulation is not a necessary antecedent to menstruation.

If this be true we might expect the occasional occurrence of intermediate types of menstruation, when (for example) some accidental upset of the ovulatory cycle sets up a stimulus to menstrual breakdown before the corpus luteum has had time to build up a completely premenstrual endometrium. Such a case, in the monkey, is illustrated in Fig. 3; the menstrual flow occurred five days prematurely, apparently as the result of an exploratory laparotomy with removal of one tube. By comparison with Figs. 1 and 2, it will be seen that the histo-

by Hartman<sup>12</sup> and several other investigators, and has been reliably reported for several other primates and Homo. (For a summary of the evidence see Hartman<sup>13</sup> and Roek, Bartlett and Matson.<sup>18</sup>) It contradicted, however, the most plausible and best attested theoretical explanation of the menstrual cycle then current, that commonly called the Schroeder-Meyer hypothesis. This conjecture, formed by experienced gynecologists who studied only human tissues, states that menstruation is caused in some way by the corpus luteum hormone, or as it would now be more precisely stated, by the withdrawal of the corpus luteum hormone. It is therefore absolutely dependent on a preceding ovulation,



Fig. 1.

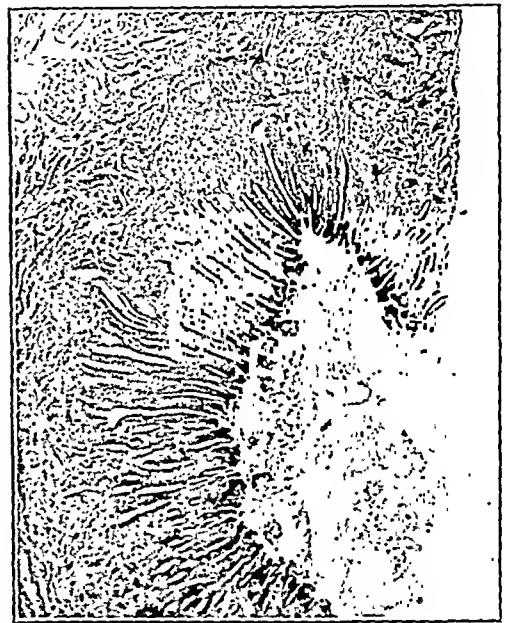


Fig. 2.

Fig. 1.—Ovulatory menstruation, second day (Macaque C.56).

Fig. 2.—Anovulatory menstruation, third day (Macaque B.128, courtesy of Dr. G. W. Bartelmez).

and is inevitably associated with a "premenstrual" state of the endometrium brought about by the corpus luteum—"Ohne Ovulation, keine Menstruation." Bleeding from the uterus, without a corpus luteum, however regularly cyclic it might be, however exactly it resembled ovulatory menstruation in all outward aspects, could not be accepted as menstruation by those who accepted the hypothesis. For them, the concept of menstruation without a "premenstrual" endometrium seemed as difficult as do some of the unfamiliar deductions from the relativity theory to those of us who learned our physics (if at all) only upon the Newtonian basis.

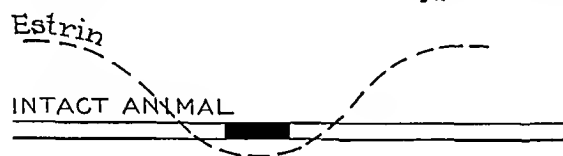
Bartelmez<sup>3</sup> pointed out that in specimens of the human endometrium obtained during menstruation, the only invariable menstrual changes



hypothesis of the same sort which was supported by experimental evidence. He found that removal of both ovaries from a mature Rhesus female will often cause within a few days a single period of menstruation-like bleeding. He then administered to the castrate monkey a course of the estrogenic hormone and found that discontinuance of the estrin also causes a period of bleeding. In another group of experiments administration of estrin was found to postpone the bleeding caused by oophorectomy.

On this basis Allen formulated the estrin-deprivation hypothesis, which suggests that natural menstruation is due to temporary cyclic reduction of the amount of estrin available in the body. Estrin is the *x*-substance of my private meditations.

### Estrin-deprivation hypothesis:



### Test of the hypothesis:

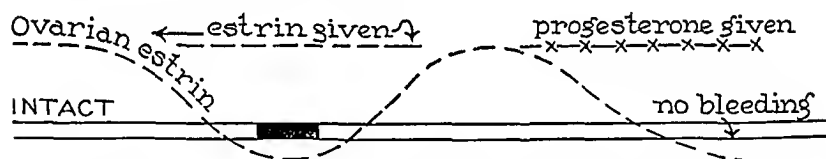


Fig. 5.—In the lower figure the natural level of estrin is shown fluctuating cyclically, not as a fact, but to show how the actual results of injecting the ovarian hormones bear on the estrin-deprivation theory (Corner, 1935; Corner and W. M. Allen, 1936).

Subsequent quantitative experiments, including especially those of Zuckerman<sup>21</sup> have shown that not only total deprivation but also mere lowering of estrin dosage below a certain level will produce the bleeding. The word "deprivation," as used in this connection, is therefore to be taken in a relative sense.

From this hypothetical explanation of menstruation, in its simple original form, it follows that if the estrin level can be maintained by administration of the hormone, natural menstruation should not occur. This I attempted in monkeys,<sup>7</sup> with negative results; that is to say, daily doses of estrone (in the form of progynon) presumably within the physiological range, did not interfere with the first menstrual period due after the beginning of the injections.

On the other hand administration of the corpus luteum hormone, progesterone, in small doses promptly inhibits natural menstruation in experimental monkeys.<sup>7, 10</sup> Smith and Engle<sup>20</sup> and Engle, Smith and Shelesnyak<sup>11</sup> found that bleeding induced in castrate monkeys by

logical state is intermediate between that of ovulatory (Fig. 1) and anovulatory menstruation (Fig. 2). Bartelmez<sup>3</sup> has described human specimens showing various evidences of menstrual changes of intermediate character.

Before the era of experiment with the ovarian hormones, it was supposed by some that the corpus luteum induces menstruation by some sort of positive effect on the uterus, its presence and activity building up the endometrium to a hemorrhagic phase. Others (e.g., L. Loeb<sup>10</sup>) with closer approach to the truth recognized that the hemorrhagic phase is related to retrogression of the corpus luteum and withdrawal of its function. To me, as I became more and more familiar with anovulatory cyclic bleeding in the monkey, and found that I could in no wise distinguish it from menstruation of the orthodox type, except by exploration of the ovaries and microscopical study of the endometrium, it seemed that any hypothesis upon which progress could be

### Removal of ovaries; estrin deprivation:

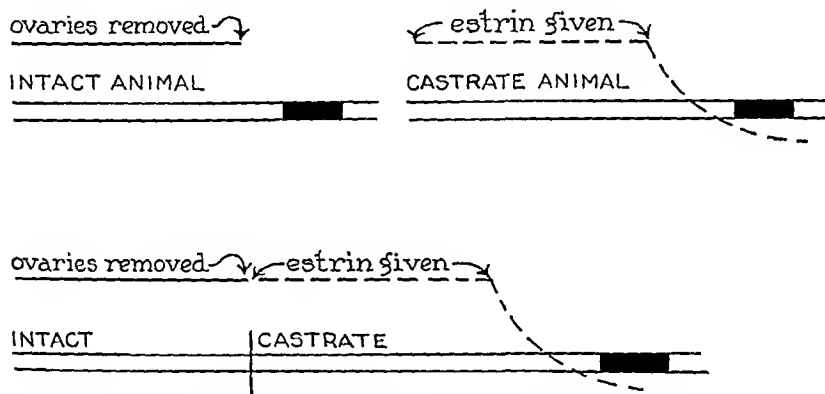


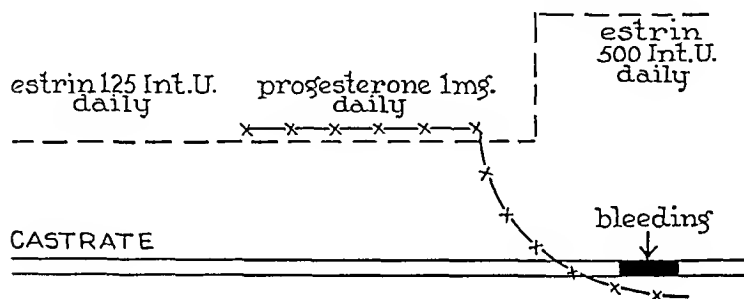
Fig. 4.—Illustrating the experiments of Allen, 1927, 1928. In this and the following graphs the black bars indicate uterine bleeding.

based must at least tentatively accept anovulatory cyclic bleeding as true menstruation. Such a hypothesis could not demand a corpus luteum and the premenstrual state as necessary, and it could only define menstruation as "periodic bleeding from the normal uterus," without further limitation. On such a hypothesis, it seemed to me that menstruation might indeed be due rather to withdrawal of some stimulus or other, than to any positive action of the corpus luteum. Leaving to the future any conjecture as to what it was that might be withdrawn when the corpus luteum retrogresses, and what when anovulatory menstruation takes place, I formulated privately what I called the "hypothesis of  $x$ -withdrawal," i.e., that menstruation is due to the withdrawal from the body of a substance the loss of which temporarily disturbs the endometrium.

I did not print the conjecture, for I had no idea what my " $x$ " might be; but a few years later, after the isolation of the estrogenic hormone by E. Allen and Doisy, Allen announced<sup>1, 2</sup> a more specific

tailed experimental analysis of this finding, and have shown that it is best explained by supposing that progesterone has the property of suppressing the effect of estrin upon the endometrium. What chemical and physiological reactions give rise to such interactions of the ovarian hormones is for the future to determine. Pincus and Zahl<sup>17</sup> and Smith and Smith<sup>19</sup> have probably obtained a clue by their studies of the metabolism of the estrogens, which show that progesterone causes an increase of total urinary excretion of estrogen and the conversion of estrone to estriol, and at the same time protects the estrogenic hormones from destruction while in the body.

### Progesterone during a course of estrin:



### Current hypothesis of ovulatory menstruation:

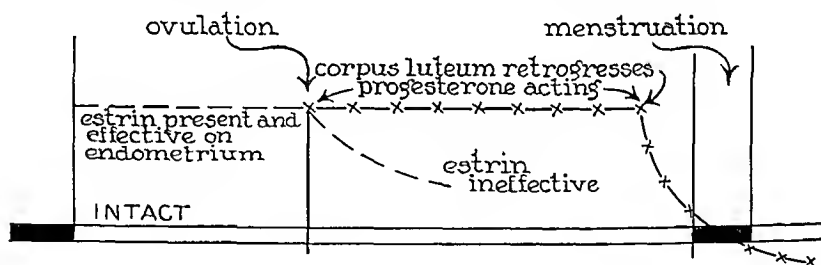


Fig. 7.—The upper figure illustrates the production of bleeding after discontinuance of a course of progesterone, in spite of continued and even more intensive estrin treatment. The dosage shown is that of the author's experiments (Corner, 1937, 1938); similar results were obtained by Zuckerman, 1937, and by Hisaw and Greep, 1938.

These facts enable us to construct a relatively simple hypothesis of the normal cycle which is really a modified form of the estrin-deprivation hypothesis.

We start with the postulate that progestin in some way or other has the property of suppressing the menstruation-preventing power of estrin, while itself holding off menstruation. Then in the normal cycle the uterus will not bleed during the first half ("follicular phase") because the ovaries are furnishing estrin. It will not bleed during the second half of the cycle ("corpus luteum phase") because the corpus luteum is furnishing progesterone. The production of estrin in all

a decidedly vigorous form of estrin deprivation (discontinuance of estrin injections with simultaneous discontinuance of gonadotropic hormone, plus castration) was prevented by crude progestin. Prevention of ordinary estrin-deprivation bleeding by the use of progesterone has been demonstrated by Hisaw<sup>14</sup> and Corner.<sup>9</sup> The discontinuance of a course of progesterone injections of suitable dosage invariably causes the menstruation-like bleeding.<sup>9, 11, 14, 21</sup> In formulating a satisfactory theory of menstruation, we must therefore take into consideration progesterone deprivation as well as estrin deprivation; the corpus luteum shares with the estrogenic endocrine tissue of the ovary the property of causing, by its abrupt removal, breakdown of the endometrium.

### Progesterone prevents estrin-deprivation bleeding:

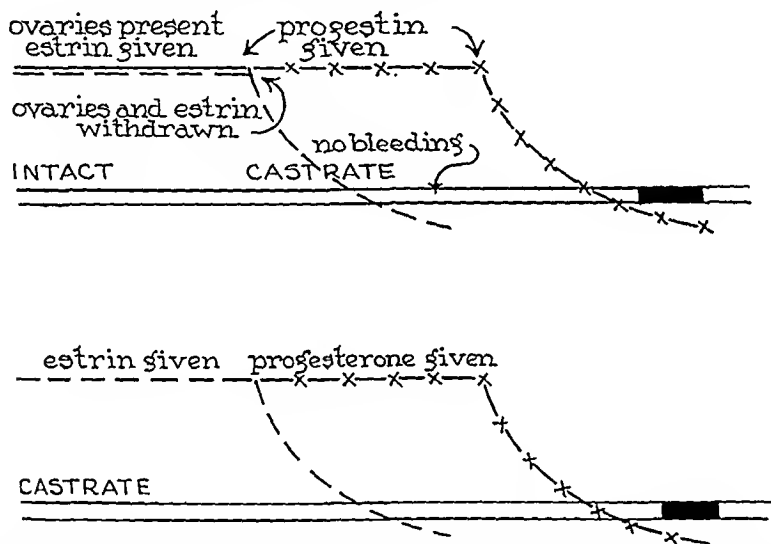


Fig. 6.—The upper figure illustrates the experiments of Smith and Engle, 1932, and Engle, Smith and Shelesnyak, 1935. The lower figure represents the results of Hisaw, 1935, and Corner, 1938. Estrin-deprivation bleeding is postponed by progesterone; discontinuance of progesterone is then followed by bleeding.

Markee states that when bleeding is produced in one of his intra-ocular endometrial grafts, by withdrawal of either hormone, he witnesses the same sequence of isehemia and hemorrhage that occurs in spontaneous menstruation.

A further step was taken in the experiments of Zuekerman,<sup>21</sup> of Corner<sup>9</sup> and of Hisaw and Greep<sup>15</sup> in which estrone was given in quantity sufficient to build up the endometrium and to cause bleeding if it had been discontinued. While this course of estrone was being given continuously, a ten-day course of progesterone was given and stopped. A few days thereafter menstruation-like bleeding began, in spite of the continued administration of estrone; in fact, bleeding could not now be prevented unless the daily dose of estrone was increased to many hundred international units. I have given elsewhere<sup>9</sup> a de-

of a corpus luteum. When ovulation does occur, however, it is geared to the fundamental cycle, and we then have premenstrual changes during the latter half of the cycle. In monkeys the menstrual cycles quite often do not reach the stage of completeness at which ovulation occurs, in humans anovulatory cycles are rare and occur most often during the earliest years after puberty and the latest before the menopause.

We are quite ignorant as to the mechanism by which a drop in hormone level causes the resultant vascular changes in the endometrium. Estrin-deprivation bleeding is an acute affair associated with an abrupt fall in level of the hormone, and it soon ceases and does not recur if the estrin level remains low. Everyone who has studied it experimentally has made conjectures involving the notion of vasoconstrictor effects produced by the deprivation, but no one has yet hit upon the intermediate steps between the estrin deprivation and the ischemic phase.

An interesting conjecture, differing somewhat from the hormone-deprivation hypothesis, has been put forward recently by Smith and Smith,<sup>19</sup> who conjecture that the bleeding of menstruation is caused not by deprivation of estrin, but by its conversion into a nonestrogenic by-product which is toxic to the endometrium. No doubt other variations upon this theme will be offered and subjected to experimental test; but all such hypotheses will agree, as I have maintained here, that menstrual bleeding is caused by fluctuations in levels of the ovarian hormones. It follows that noncyclic and therefore pathological bleeding may also be caused by defectiveness, in amount, proportion or kind, of these hormones. This etiologic concept taken alone will perhaps be acceptable to all, but taken in connection with the strict corpus luteum theory of menstruation, it leads to a conclusion unacceptable under that hypothesis; for it tells us that after all there are not two different and distinguishable kinds of bleeding from the uterus, namely the normal and cyclic kind called menstruation, and the irregular or continuous kind called pathologic under various names such as menorrhagia and metrorrhagia. When the existence of anovulatory menstruation was first proved in the monkey, and suspected in the human, it was easy, but it was wrong, for objectors to call that kind of menstruation "pathologic bleeding" as if a sharp line could be drawn. The modern hypothesis hints to us that much of the functional pathologic bleeding is due to hormone deprivation or imbalance, and therefore we must expect a series of types of hemorrhage from normal menstruation through every grade of disturbance to the most severe metrorrhagia. That clinical studies based on this idea are already hopefully under way is shown by such work as that of Smith and Smith,<sup>19</sup> presented at the 1938 meeting of the American Gynecological Society. Such progress is ample recompense for the abandonment of an untenable theory, for it bids us hope that those same hormones that control the normal cycle will help us to control its aberrations and at last to banish the spectre of uterine hemorrhagic disease.

probability continues. By our assumption, however, the corpus luteum is suppressing the protecting effect of estrin; therefore when the corpus luteum undergoes retrogression, the animal is suddenly deprived of the action of both estrin and progesterone, and the endometrium breaks down. Ovulatory menstruation is thus a special case of estrin-deprivation bleeding.

This explanation of the normal cycle is not contradicted by any known facts. It will be observed that it does not necessarily call for a rise and fall of estrin production by the ovaries, for the cyclical presence and absence of the corpus luteum is sufficient to cause a periodic phase of ineffectuality of estrin upon the endometrium.

This scheme does not of course explain anovulatory menstruation. In anovulatory cycles there is no coming and going of the corpus luteum to cause hormone deprivation. Indeed in the monkey I have not been able to see any change in the ovary that can be correlated with the onset of anovulatory menstruation as we can correlate retrogression of the corpus luteum with ovulatory menstruation. One might expect to find beginning atresia of a large follicle, or some comparable histologic cause of estrin deprivation, but I have compared in detail, in serial sections, the ovaries of two monkeys killed during actual anovulatory menstruation with two killed during the interval of the anovulatory cycle, and have not detected any significant difference. It is, however, conceivable that fluctuations of estrin level can occur without morphologic variation in the ovary, and perhaps it will turn out in the end that the give and take of the pituitary-ovarian (or of the pituitary-ovarian-adrenal) relationship does produce in cyclic fashion an actual estrin deprivation. In this case anovulatory menstruation should be preventable by administration of estrin. To test the matter by experiment in monkeys will be tedious indeed, for the time of year when anovulatory cycles prevail is also a time of menstrual irregularity. It will be necessary to prove the absence of a corpus luteum by surgical exploration, then to administer the estrin; but if menstruation fails to occur its absence might be due to the experiment or it might be merely summer amenorrhea. A long series will be required to be significant. Meanwhile we might well keep in mind other possibilities, for example the production in the ovaries of small quantities of progesterone-like or androgen-like hormones, which might counteract estrin in the anovulatory cycle as we suppose progesterone to do in the ovulatory cycle.

This last is pure conjecture; what I hope has been clearly brought out is the probability that hormone-deprivation is the cause of cyclic uterine bleeding, and the fact that the presence of a corpus luteum is not essential for menstruation.

We may suppose that there is a fundamental cycle of pituitary-ovarian balance, which in primates causes periodic uterine hemorrhage, whether ovulatory or anovulatory. As Hartman<sup>12</sup> has pointed out, this cycle may or may not reach its fullest development, which is characterized by maturation of an ovarian follicle and the formation

## BRENNER TUMORS OF THE OVARY\*

### WITH REPORT OF 14 NEW CASES

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THE difficulties in the classification of ovarian tumors, especially of the malignant group, are notorious. They are due chiefly to our ignorance of the histogenesis of many types. As a matter of fact, most of the classifications which have been suggested have been based upon general pathologic criteria, plus the enumeration of certain special varieties in which something definite is known as to origin and special characteristics. The Krukenberg tumor is a good example of this group. In recent years it has been possible, chiefly through the work of Robert Meyer, to sift out an important group of tumors which have the common characteristic that they arise from rests developing in the early stages of ovarian development. Another characteristic is the fact that, taken as a group, they are far less malignant than other varieties of ovarian cancer. There is an obvious practical importance in separating out such a group, from the standpoint of prognosis and mortality statistics.

One member of this group of so-called special ovarian tumors, the granulosa cell carcinoma, is relatively frequent, constituting something like 10 per cent of all primary ovarian cancers, so that any comparatively small series of cases of ovarian cancer in which a considerable proportion of granulosa cell tumors happens to be included might well give a less pessimistic impression of the degree of malignancy of ovarian carcinoma than most of us have. The other members of the group, dysgerminoma and arrhenoblastoma, are much less frequent, but they likewise are characterized by relatively low degrees of malignancy.

In former years this special group was made to include a fourth tumor type, the so-called Brenner tumor, but the rather different mode of histogenesis of this neoplasm and the fact that it is essentially benign would seem to necessitate its separation from the other members of this group. The fact that most general pathologists and many gynecologic pathologists are not familiar with this tumor variety, and that it is frequently confused with granulosa cell carcinoma, makes it worth while to discuss its characteristics on the basis of the comparatively large group of cases which we have encountered in our laboratory.

This paper is based upon the study of 17 cases, though only 14 are reported herein, since 3 cases have been previously published (Wolfe and Kaminester,<sup>1</sup> Bland and Goldstein,<sup>2</sup> Te Linde<sup>3</sup>). Most of the cases in our series have been encountered in recent years, though it is certain that many instances must have been overlooked in the earlier years of

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## SUMMARY

In castrate monkeys menstruation-like bleeding is caused by sudden discontinuance of a course either of estrogenic hormone or of progesterone. When the estrogen and progesterone are given simultaneously in suitable amounts, bleeding occurs if the progesterone is discontinued even though sufficient estrogen to prevent bleeding is still being administered. This observation offers a possible explanation of natural menstruation on the basis of recurrent action and inaction of the corpus luteum. Anovulatory menstruation offers a more obscure problem. The mechanism by which deprivation of the hormones sets up a disturbance of the endometrial blood vessels is still unexplained.

From these considerations it is probable that pathologic uterine bleeding may be caused by fluctuations in levels of the ovarian hormones, and that no sharp distinction exists between menstruation and functional metrorrhagia. Such a concept opens the possibility of ultimate control of uterine hemorrhagic diseases.

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nests, and because of the superficial resemblance of the latter themselves to follicles. The condensed ovarian tissue about the cell islands was even interpreted as representing the theca folliculi. Meyer's explanation of the histogenesis of these tumors, while difficult of proof, has been accepted by practically all subsequent writers as probably correct. According to this view, the tumor arises from the islands of indifferent cells first fully described by Walthard<sup>10</sup> in 1903, though Plaut<sup>11</sup> credits Werth with an earlier description as far back as 1887. Akagi,<sup>12</sup> a pupil of Walthard, restudied the problem in 1928, his findings being essentially like those of Walthard himself.

The Walthard inclusions may be found in the superficial portion of the ovaries, and even more frequently, the tubes and uterine ligaments, especially in the newborn and young child, but occasionally in the adult. They may consist of nests of cells resembling squamous epithelium, often showing cystic hollowing, and perhaps actually converted into tiny cysts (Fig. 1). On the other hand, the inclusions



Fig. 1.



Fig. 2.

Fig. 1.—Walthard islets, resembling plaques of squamous epithelium, on surface of ovary near hilum. In the medulla of this same ovary (Case 5) a small Brenner tumor was found.

Fig. 2.—Walthard island at another portion of same ovary shown in Fig. 1. This likewise was near hilum, and it appears as an acinus-like space lined by columnar epithelium.

may take the form of glandlike spaces lined by columnar, perhaps ciliated, epithelium, with at times definite mucoid activity (Fig. 2). In other words, the transmutations of the epithelium are much like those exhibited by the epithelial nests of the Brenner tumors, constituting at least circumstantial evidence of an origin of the latter from the Walthard rests. In addition to the embryologic rests described by Walthard, one must consider the possibility that Brenner tumors may arise from the areas of epithelial metaplasia found not infrequently on the surface of the ovaries which are the seat of chronic peri-oophoritis. One often sees striking metaplasia of the peritoneum and germinal epithelium under such circumstances, with at times the formation of areas of stratified epithelium, not infrequently cystic, and quite like the Walthard islands of indifferent cells (Fig. 3). Whether such islands can be the starting-point of Brenner tumors is a question, though a number of authors have suggested this possibility.

Another possible source has been suggested by Schiller,<sup>13</sup> chiefly on the basis of the microscopic study of one of the cases reported by him in 1934. In this

our laboratory, when this now clearly delineated neoplastic type was rather generally unrecognized.

The first description of what was undoubtedly a Brenner tumor appears to have been by Orthmann<sup>4</sup> in 1899, at least eight years before the publication of Brenner.<sup>5</sup> He applied to the tumor in his case the designation of "fibroma papillare superficiale carcinomatosum ovarii," and it is of interest that in this first description the suggestion is made that the origin may be in the cell aggregations which we now speak of as Walthard islets, thus anticipating the prevalent modern viewpoint as to the histogenesis of these tumors. The designation of the tumor as "papillary" is difficult to understand except that the author evidently related his tumor, which happened to be superficially placed, to the not infrequent superficial fibroadenomas, which frequently are papillary.

The three cases reported by Brenner in 1907 were designated by him as "oophoroma folliculare" and were confused by him with the granulosa cell tumors included in the same report. This confusion is still quite commonly encountered in laboratories of pathology. Brenner's employment of the term oophoroma was based on the idea that the swollen cells found so often in the interior of the epithelial nests which characterize the Brenner tumor are of the nature of ova, a morphologic misinterpretation similar to that which has been made in the case of certain other ovarian tumors, such as the so-called "medullary carcinoma with ovum-like cells."

It was Robert Meyer<sup>6</sup> who in 1932 described the characteristics of the Brenner tumor, distinguishing it sharply from granulosa cell carcinoma, and offering the explanation of histogenesis which is still the generally accepted one. In his analytical review of the literature, he was able to eliminate from this category certain cases which had been reported as Brenner tumors, and to add others which had been incorrectly reported under other designations. With his own 4 cases, he was able thus to collect a total of 22 cases. The first American case, so far as I can ascertain, was that of Geist,<sup>7</sup> reported in 1922, although it was not definitely classified by the author.

*Incidence.*—It is of interest to note that the three cases reported by Brenner in his original paper of 1907 were all observed by him within a period of one and one-half years, which would give a false impression of the frequency of this neoplasm. Meyer encountered only 4 cases in the large material of his laboratory during twenty years, and von Szathmáry<sup>8</sup> more recently reported an incidence of 5 cases among 1,114 ovarian tumors in the Budapest Clinic during fifteen years. In our own laboratory we have observed 17 instances, in a material of more than 48,000 case specimens, though a further review of all this material would undoubtedly reveal many more. On the other hand, it must be added that several of our cases were slides or specimens sent in to us from other clinics for diagnosis. The tumor must, therefore, be looked upon as a very rare one, though with other commonly unrecognized types, not nearly so rare as the literature would indicate. Meyer, in 1932, was able to collect only 22 cases, but in 1933 Szathmáry collected 40, including 5 of his own, and in the most recent review of the subject, that of Varangot<sup>9</sup> (1938), 108 cases were collected, including the 3 reported by the author himself. Our 14 new cases would raise this to 122.

*Histogenesis.*—The most interesting aspect of the Brenner tumor is the question of its histogenesis. As already mentioned, Brenner himself believed the source to be the follicle, because of the ovum-like structures seen so often within the cell

matter of fact, trace all transitions from mere Walthard rests which are not Brenner tumors, to those in which there is only slight surrounding fibromatous reaction and nodule formation, to the larger tumors in which both epithelial and fibromatous elements are present in large amount.

*Clinical Characteristics.*—Brenner tumors of the ovary occur most frequently in women beyond the menopause, the usual statement being approximately correct, that more than 50 per cent occur beyond the age of 50. The ages of the patients in our own series were as follows: 71, 25, 37, 43, 36, 49, 28, 37, 45, 45, 62, 63, 27, 35. The oldest patient was therefore 71, and the youngest 25. So far as I know, no genuine Brenner tumor has been reported in a child. In our own series, therefore, the age range is definitely lower than that commonly reported, only 3 of our 14 patients being more than 50 years of age. This is probably to be explained by the fact that a considerable proportion of our tumors were very small, being discovered incidentally, either at operation or in the laboratory in patients operated upon for other lesions. In contrast with other tumors of the ovary, certainly those

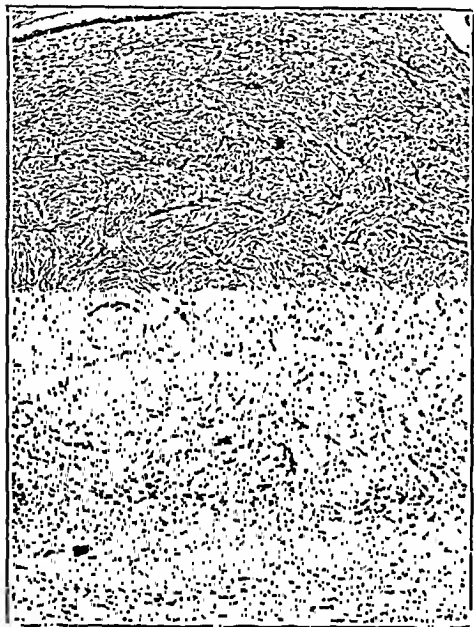


Fig. 5.



Fig. 6.

Fig. 5.—Definitely cortical Brenner tumor, only a few millimeters in diameter, just beneath germinal epithelium of cortex (Case 7).

Fig. 6.—Typical histologic picture of solid Brenner tumor (Case 6).

of malignant type, the growth of Brenner tumors is likely to be slow. Furthermore, they produce no very characteristic symptoms, so that the high incidence in elderly women loses some of its significance, as the tumors which come to removal might well have been present for a good many years. Ascites seems to be rare, though it was noted in one of our cases (Case 9). Eleven of our 14 patients were white, 3 colored. Three (Cases 2, 13, and 14) were pregnant at the time of operation. The menstrual history is not at all characteristic, and in our premenopausal cases the occasional abnormality was obviously due to associated lesions and not to the tumors. Endometriosis was an associated finding in 1 patient (Case 5).

*Pathology.*—The size of the tumors varies between very wide limits. Some are of microscopic size, while others may assume enormous proportions, even when not associated with cystadenoma. The largest solid Brenner tumor recorded appears to be that of Neimann,<sup>15</sup> which weighed 15 pounds, and which, to judge from the description and illustration, is a genuine tumor of this variety. The gross appearance of the solid tumors is quite similar to that of fibroma, although there is frequently

case he found what he interprets as an abnormal persistence of the embryonic relationship between the rete ovarii and the epoophoron tubules in the hilum of the ovary. If one accepts the view held by some that these two structures have a totally different origin, the epoophoron tubules from the Wolffian body and the rete from the germinal nucleus, it would be difficult to explain any very intimate relationship. On the other hand, the present-day tendency is to accept the view championed by Fischel,<sup>14</sup> and others that most of the ovarian components, including the medullary tubules, the granulosa and even the epoophoron tubules, are derivatives in situ of the mesenchyme. Schiller therefore postulates that if Wolffian epoophoron tubules, developing in the neighboring Wolffian body mesenchyme, are included in the ovarian hilum, they possess the potentiality to form epithelium like that which normally characterizes the urinary tract. In other words, Schiller, rather laboriously, as it seems to us, compares the epithelial variations in Brenner tumors, including even the pseudomucinous changes so often seen, with those to be found in the urinary tract.

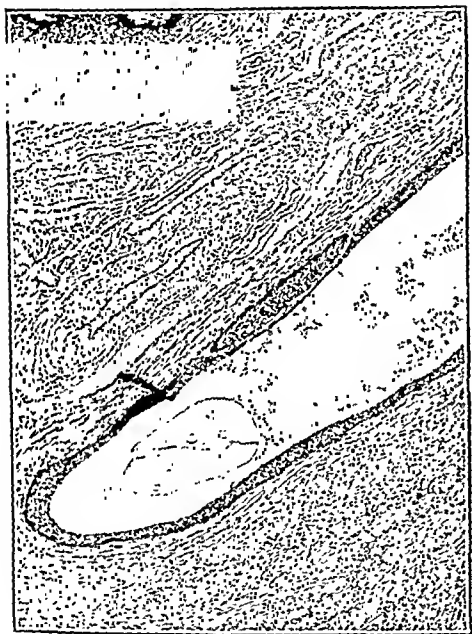


Fig. 3.



Fig. 4.

Fig. 3.—Squamous metaplasia of peritoneal cleft in adhesions between tube (left) and ovary (right).

Fig. 4.—Small medullary Brenner tumor in Case 3.

Schiller is careful to say that his explanation of the origin of some Brenner tumors does not conflict with the more generally accepted viewpoint of Meyer, above discussed, suggesting that different Brenner tumors may have different origins. He offers as further evidence of his hypothesis the fact that the local topography of some Brenner tumors indicates an origin from the hilum. This may be freely admitted, for certainly at least some of these neoplasms, as shown for example in our Cases 3, 4, and 5, do arise in the hilum (Fig. 4). On the other hand, frequently they are cortical, as in our Cases 7, 8, and 13. The seat of origin of such tumors can naturally be best studied in very small growths, for in the large tumors, or those associated with large cysts, the normal ovarian geography is usually blotted out. It would be difficult, as well as unnecessary, to invoke Schiller's theory in the explanation of such a tumor as that shown in Fig. 5, which is located just beneath the surface of the ovary. Moreover, Walthard islands may be found in the region of the mesovarium as well as in other parts of the ovary, so that it seems to us that Meyer's theory is still the one supported by the best evidence. One can, as a

ovum that these tumors were originally designated by Brenner himself as oophoroma folliculare. The slightly condensed surrounding ovarian tissue layer was even thought to represent the theca folliculi.

When, as is frequently the case, the central liquefaction is more advanced, the entire nest may be converted into a tiny cyst with little or none of the original epithelium left, though most often a number of layers persist. Meyer and others have called attention to the difference between the innermost layer of the epithelium in these partially cystic nests, and the corresponding layer in the folliculomatous variety of granulosa cell tumors. In the former the nuclei are placed peripherally, i.e., away from the lumen (Fig. 7) while in granulosa cell tumors they are at the central pole of the cells. On the other hand, in many of the cell aggregations which show central liquefaction, the cavity is lined irregularly by degenerating cells rather than by any well-ordered layer.

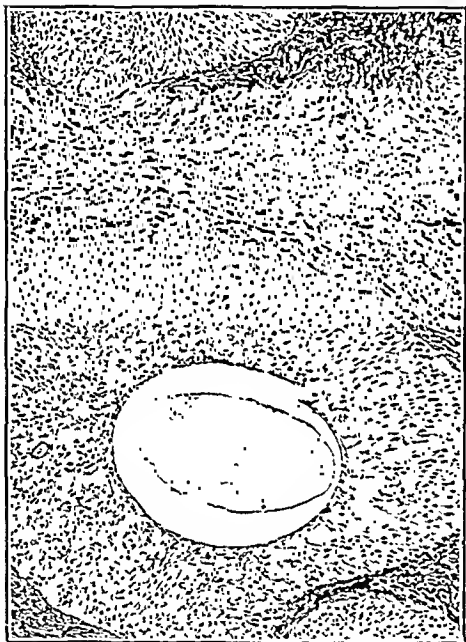


Fig. 9.



Fig. 10.

Fig. 9.—Ovumlike appearance of degenerated protoplasmic center of partially cystic epithelial nests (Case 6).

Fig. 10.—Pseudomucinous columnar epithelium lining cystic center of cell nest (Case 11).

The most interesting feature of the epithelium, however, is the fact that its superficial layer, in the small cystic cavities, so common in the cell nests, may assume a mucoid columnar form quite like that which characterizes the ordinary pseudomucinous variety of cystadenoma (Fig. 10). There is thus produced a superficial resemblance to a many-layered gland ("intra-epithelial gland"). This was described by Geist as far back as 1922, although this observation appears to have been overlooked by subsequent writers. Meyer and von Szathmáry find that this inner layer of cells contains glycogen, which, incidentally, is not found in granulosa cell tumors. The latter, on the other hand, show lipoid material, which is lacking in the Brenner tumors. The fluid content of the cystic cavities of the latter is of either mucoid or colloid nature, or may be a combination of these.

One can see in one and the same section solid epithelial nests, those with a superficial layer of pseudomucinous epithelium lining the small central cavities, and areas in which the pseudomucinous epithelium alone is to be seen lining gland like spaces and perhaps large cystic cavities (Fig. 11). The latter, in other words,

a yellowish tint to the cut surface. There is very little tendency to necrosis or cystic degeneration in the solid variety, and hemorrhage is uncommon. No definite capsule exists, although the surrounding ovarian stroma is more or less compressed.

From a microscopic standpoint there are two essential constituents, viz., the characteristic nests of epithelial cells and the fibromatous connective tissue groundwork surrounding the epithelial islands (Fig. 6). Both of these must be present to justify the diagnosis of Brenner tumor, a fact overlooked by some authors who apply the term to the epithelial rests themselves. This mistake, for example, was made by Plaut, whose Cases 6, 7, and 8 do not seem, for the above reason, to be properly classed as Brenner tumors. Why the fibromatous reaction occurs with some rests and not others can be explained only on the general basis of the cytogenous influence (Fischel) exerted by the epithelium not only in Brenner tumors but also in other conditions, such as endometriosis. With the latter, the endometrial epithelium excites an endometrial stromalike reaction about the glands, though in some cases this may be absent.



Fig. 7.



Fig. 8.

Fig. 7.—Unusually bulky epithelial fields in Brenner tumor (Case 1). Note the columnar epithelium, with peripheral nuclei, in the small cystic cavity toward top (see text).

Fig. 8.—Cystic hollowing of epithelial islands in medullary Brenner tumor of Case 5.

The epithelial nests may be round or cylindrical, very small or extremely bulky, as in some of our cases (Fig. 7). The striking characteristic is the uniformity of the cells. In many islands even the cells close to the connective tissue margin lack the compactness and the intensity of nuclear staining seen in ordinary epithelial neoplasms, malignant or benign. In others they do seem slightly more closely packed. The cells are rather large and polyhedral, with small nuclei of ovoid shape and striking uniformity, and with no suggestion of overactivity, so that they do not in any way suggest malignancy. The term *carcinoid* as applied to these tumors by Frankl<sup>16</sup> is not a good one, except perhaps as referring to the distribution of the nests in the connective tissue stroma.

In most tumors there is some tendency, often very widespread, to central cystic degeneration of the epithelial nests (Fig. 8). In the early stages of this there results a small central cavity filled with a rounded protoplasmic mass which superficially resembles an ovum, and which was so interpreted by the earlier writers (Fig. 9). For example, it was because of this resemblance to a follicle with central

a careful study of many supposedly simple fibromas of the ovary would show them to be of the Brenner variety.

As I have already mentioned, the Brenner neoplasm is to be looked upon as benign. There was a tendency not so many years ago to class them with the malignant tumors of the ovary, perhaps because of their earlier confusion with granulosa cell tumors. Not a single case in the literature, however, has recurred after removal, though Mandelstamm<sup>17</sup> cites an instance reported by Tavildaroff, in a rather inaccessible Russian source, of a Brenner tumor which is said to have recurred in the other ovary. This case seems very doubtful, and, if it really was a Brenner growth, was more likely to have been an instance of bilateral tumor. Similar bilateral tumors have been reported by Schiffman<sup>18</sup> and others.

*Absence of Endocrine Influence.*—A point which has received some discussion is as to the influence, if any, of these tumors upon the endometrium. The capacity of the granulosa cell tumor to produce hyperplasia of the endometrium and menstruation-like bleeding in postmenopausal women is well-known, and is readily explainable by their histogenesis and their capacity to produce the estrogenic hormone. Only Schiffman seems to have noted hyperplasia of the endometrium and uterine bleeding in association with Brenner tumors, and his illustrations would seem to bear this out. However, this isolated observation loses its significance now that we know that hyperplasia of the endometrium may at times be found in post-menopausal women in the entire absence of any tumor, and that it may be clinically associated with uterine bleeding. For this reason we have likewise had to modify our former view that the finding of well-marked hyperplasia of the endometrium long after the menopause is presumptive evidence of granulosa cell carcinoma, even though no tumor is palpable. Since there has been no confirmation of Schiffman's observation by other authors, it seems highly probable that the endometrial hyperplasia found in his case was coincidental, and that it was not causally related to the Brenner tumor in the ovaries.

In only one of our own cases (Case 12) was postmenopausal bleeding seen in association with a Brenner tumor, though unfortunately in this case the endometrium was not available for study. Moreover, in this case there was present a large pseudomucinous cystadenoma. As in Schiffman's case, and for the same reason, it seems likely that the bleeding in our patient was probably not related to the presence of the Brenner tumor. Postmenopausal bleeding is said to have occurred likewise in a number of other cases in which the endometrium was not studied (Schiller, Abraham,<sup>19</sup> Kleine,<sup>20</sup> Freund,<sup>21</sup> Fauvet<sup>22</sup>) but in spite of this there is no reason to think that this was due to any such direct endocrine effect upon the uterus as is produced by the granulosa cell tumors. As a matter of fact, the uterus in old women with Brenner tumors has often been described as typically senile and atrophic. When the tumor occurs during the menstrual life, no characteristic effect upon menstruation is noted, as I have previously mentioned.

#### CASE REPORTS

CASE 1.—(Gyn. Path. 47851.) For the privilege of including this case in our series we are indebted to Dr. S. A. Chalfant, of Pittsburgh. The patient was 71 years old. A normal menopause occurred at 54, and there had been no bleeding since. There had been no pregnancies. A large tumor in the lower abdomen had been noticed by the patient several months before admission.

Operation revealed the tumor to be a large cystic growth of the right ovary, measuring 19 cm. in diameter. About half of this tumor was represented by a thin-walled cyst with smooth lining, while the remainder was solid, presenting a dense structure resembling fibrous tissue, arranged in interlacing bundles, and containing small spicules of calcified material. The solid fibrous portion was grayish in color, with blotchy areas of light yellow, and there were a number of tiny cystic areas.

Microscopically this case presents a beautiful illustration of transitional changes between a solid Brenner tumor and a pseudomucinous cystadenoma. The solid parts of the tumor show the characteristic epithelial nests embedded in large areas of fibromatous stroma. In places, however, the nests show hollowing, with an inner



present the characteristic picture of pseudomucinous cystadenoma, and, as a matter of fact, large cystadenomas may thus arise, with perhaps no trace of their original source other than a small nodular thickening in which the typical Brenner pattern may still be preserved. There is no doubt, therefore, of the correctness of Meyer's observation that at least a certain though small proportion of pseudomucinous cystadenomas have their origin in Brenner tumors, though the majority no doubt are to be interpreted as teratomas in which certain entodermic elements have blotted out other constituent tissues, just as in struma ovarii it is the thyroid tissue which has overridden and blotted out other teratomatous elements.

There is logic, therefore, in the subdivision of Brenner tumors into the solid and cystic varieties, though it should be remembered that the subdivision is not a sharp one. In other words, even in the solid tumors some degree of pseudomucinous epithelial change may be seen, while in even the large cysts, solid Brenner rests may be found in nodular masses persisting in the cyst wall. Meyer states that serous cystadenomas of the ovary may likewise at times have a similar origin from Brenner tumors, though we have observed no cases of this type.

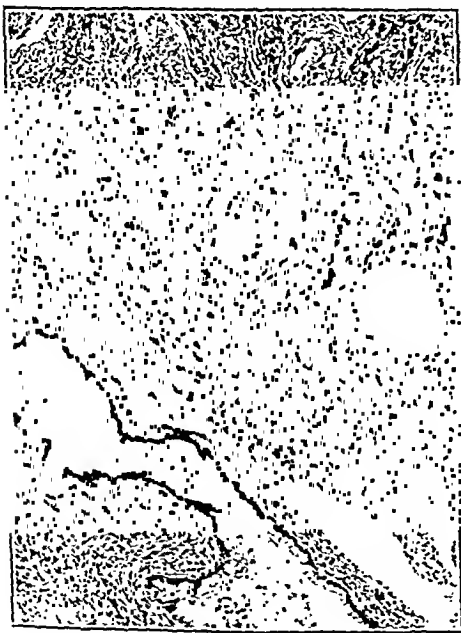


Fig. 11.

Fig. 11.—Pseudomucinous transformation of Brenner rests passing on by easy transition into a large pseudomucinous cystadenoma, part of whose wall is seen below and to left (Case 1).

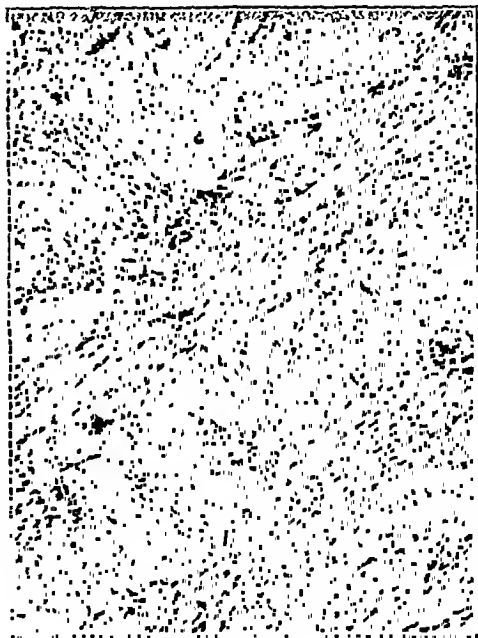


Fig. 12.

Fig. 12.—Typical epithelial islands in large ovarian fibroma of Brenner origin (Case 10).

Not only cystadenoma of the ovary, but likewise fibroma may have its origin in Brenner tumors. From time to time in past years solid fibromas have been reported to show epithelial aggregations which have been variously interpreted. Frankl in 1927 reported a group of such cases to which he applied the designation of fibroadenoma ovarii adenocysticum, but, as Meyer has shown, these are properly to be construed as Brenner tumors in which the characteristic connective tissue response has assumed huge proportions, so that tumors weighing many pounds may be produced. The 15-pound tumor reported by Neimann belongs to this group, as does our Case 10, in which the tumor was likewise of large size (Fig. 12). In this case only a moderate distribution of epithelial nests was to be noted in the fibromatous matrix, but in that of Neimann the proportion of epithelium to connective tissue was much greater, if one may judge from the illustrations. The gross picture of Brenner tumors is quite similar to that of fibromas, and there is little doubt that



hysterectomy and bilateral salpingo-oophorectomy. The right ovary was twice the normal size, and consisted chiefly of a circumscribed nodule which on section was uniformly whitish in appearance. The microscopic picture was that of a typical Brenner tumor.

CASE 7.—(Gyn. Path. 43211.) This patient was colored, aged 28 years, and had had no pregnancies. Her complaint was of a hard mass in the lower abdomen, with pain and leucorrhea, but with no menstrual excess. On April 16, 1936, a supravaginal hysterectomy with left salpingo-oophorectomy was performed, the ovary on this side being large, adherent, and cystic, while the right adnexa were normal. In the routine pathologic examination, a tiny but typical Brenner nodule, from the standpoint of both cell islands and fibromatous stroma, was found just beneath the cortex (Fig. 5). On the surface of the ovary, overlying the nodule, there was a layer of adhesions, and the germinal epithelium beneath these had become tall and columnar, so that it resembled endometrial epithelium. This is a not uncommon finding in cases of peri-oophoritis. The very definitely cortical location of the Brenner nodule in this case would seem to rule out entirely any such explanation as that suggested by Schiller in the case of medullary tumors.

CASE 8.—(Gyn. Path. 38151.) This specimen was sent to the laboratory by Dr. Elbert DeCoursey, Ancon, Canal Zone. It was accompanied by the following clinical note from Dr. DeCoursey. "Operation: Salpingo-oophorectomy, right. The specimen comes from the ovary of a 37-year-old black female who has complained of pain in the right pelvic region. She missed the January menstrual period, but menstruated February 18, and passed some blood each day until March 9. No bleeding since that time. A large mass was palpated in the right side of the abdomen. The surgeon at Colon informs me that the patient had a ruptured ectopic pregnancy, and he excised the right tube and ovary. When I saw the tissue, the thickened right tube had been ruptured, leaving an oval bloody cavity about 5 cm. in length. I have searched, but have been unable to find chorionic villi in multiple sections. In the ovary was a round pearly pink mass about 2 cm. in diameter. It was hard, circumscribed, and seems to be well encapsulated." The "round pearly mass" proved to be a Brenner tumor which apparently had its origin in the cortical zone.

CASE 9.—(Gyn. Path. 39196.) For the sections of this case and for permission to include it in our series, we are indebted to Drs. L. C. Scheffey and Crawford of Philadelphia. The patient, aged 45 years, para i, was admitted to Jefferson Medical College Hospital, April 29, 1929, with a complaint of lower abdominal discomfort of four weeks' duration. She had noticed an enlargement of the abdomen. Menstruation had been normal except for a period of several months when the period had become shortened to two or three weeks. There had been a period of amenorrhea for three months preceding the last menstruation, which occurred one month before operation. Examination showed a nodular mass in the lower pelvis, apparently springing from the adnexa, as the uterus was small and freely movable. The patient stated that the lump felt "like a bag of marbles." At operation by Dr. Scheffey, on May 6, 1929, the tumor was found to be a solid neoplasm of the left ovary. A moderate amount of ascitic fluid was present. The right tube and ovary were normal. Supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed. The patient was apparently well eight years later.

Dr. Scheffey was good enough to send us a section of the tumor, which at that time we incorrectly diagnosed as folliculoma. On subsequent review, however, the tumor was found to be a typical Brenner tumor of the solid variety.

CASE 10.—(Gyn. Path. 42248.) This patient was colored, aged 45 years, and was admitted Aug. 8, 1935, because of a large mass extending to the umbilicus, her chief symptom being profuse menorrhagia. At operation a few days later the uterus was found to be about normal in size, though it showed several small intramural myomas. Attached to the fundus by a definite pedicle was a large solid tumor of the right ovary, the tube being normal. The tumor was 13 cm. in its

lining of tall mucoid epithelium, which in adjoining areas completely replaces the stratified epithelium, becoming more and more adenomatous, presenting the characteristic picture of pseudomucinous cystadenoma, as seen in the large cyst making up about half the entire tumor.

CASE 2.—(Gyn. Path. 47264.) For the slide of this tumor, and for permission to include the case in our series, we are indebted to Dr. D. R. Meranze of Mt. Sinai Hospital, Philadelphia. The patient was 25 years old, and she was pregnant four months at the time of operation, her complaint being of abdominal pain for two weeks preceding the latter. The previous menstrual history had been entirely normal. Before operation a large tumor was palpable in the right lower abdomen, and this proved to be a solid ovarian tumor about the size of a grapefruit. Microscopically it is a typical fibroma of the ovary, throughout which are discretely scattered large numbers of the characteristic epithelial nests which indicate the Brenner nature of the neoplasm.

CASE 3.—(Gyn. Path. 47031.) This patient was 37 years old, and was operated upon in the Gynecological Clinic of the Johns Hopkins Hospital for the removal of a large myomatous tumor, associated with extensive bilateral adnexitis. Supravaginal hysterectomy with bilateral salpingo-oophorectomy was performed. The routine laboratory examination revealed, only on microscopic examination, a tiny but perfectly typical Brenner nodule situated in the region of the right ovarian hilum. The characteristic cell nests, the fibromatous stroma and the definite pseudoencapsulation of the nodule would seem to leave no doubt as to the nature of this microscopic neoplasm (Fig. 4). No epoophoron or rete tubules could be demonstrated in relation with the tumor.

CASE 4.—(Gyn. Path. 45109.) This patient, aged 43 years, was operated upon by one of us (E. N.) at Bon Secours Hospital for chronic pelvic inflammatory disease. She had had no menstrual period for one year. Aside from the bilateral salpingitis, the left ovary was found to be moderately enlarged, measuring 4.5 by 3.5 by 2.5 cm., and the cut section showed a small, solid, circumscribed fibrous mass surrounded by a capsule of normal-looking ovarian tissue. The tumor seemed undoubtedly to arise in the medullary portion of the ovary. Its structure was that of a typical Brenner tumor of the solid type. No pseudomucinous alteration of the epithelium was to be seen.

CASE 5.—(Gyn. Path. 44210.) This patient, aged 36 years, was operated upon Dec. 3, 1936, because of large uterine myomas, associated with pelvic endometriosis and bilateral endometrial cysts. Menstruation was normal in every way, the patient entering the clinic because of lower abdominal discomfort and because she had noticed a mass in the lower abdomen. A supravaginal hysterectomy with bilateral salpingo-oophorectomy was done.

In addition to the myomas and the endometrial cysts, which need not be described in detail, the routine microscopic examination revealed a tiny microscopic Brenner tumor, measuring 1 by 0.5 mm. in the medulla of one ovary. Fig. 8 will show how typical it is, with the characteristic cell nests embedded in a circumscribed nodule of fibrous tissue arranged in an interlacing whorllike fashion. It is of great interest that in the same section one finds a number of typical Walthard cell nests on the surface of the mesovarium, some of them being of the more common squamous appearance, with cystic hollowing of the interior (Fig. 8), but others appearing as gland lumina lined by tall and partly ciliated epithelium (Fig. 2). This is the only case in which we have found Walthard islets in association with an actual Brenner tumor, and the fact that both are found in the vicinity of the hilum would seem suggestive. Moreover the presence of extensive ovarian endometriosis in this case would seem to indicate a strongly metaplastic tendency, at least to those of us who believe in the doctrine of coelomic metaplasia as the probable explanation of endometriosis.

CASE 6.—(Gyn. Path. 42178.) This patient was 49 years old, a para ii, whose menstruation had been entirely normal in character and amount, and who was operated upon because of large uterine myoma, the operation consisting of supravaginal

pregnancy, though this is not certain. The operation consisted of supravaginal hysterectomy and bilateral salpingo-oophorectomy.

Examination of the specimen in the Carnegie Laboratory showed the uterus to be 65 by 58 by 58 mm. in size, with an implanted ovum, apparently beginning to dislodge, 50 by 20 mm. The left ovary contained a dermoid cyst about 11 by 11 cm., while in the right ovary there was a firm rounded nodule about 15 mm. in diameter near one pole, extending from the medulla to the surface, so that it was difficult to say whether it originated in the cortex or the medulla. Its microscopic examination showed it to be a typical Brenner tumor of the solid variety.

#### SUMMARY

This paper is based upon the study of 17 cases of Brenner tumor of the ovary, including the 14 new cases herein reported. This brings the total of reported cases to 122, though new instances are being reported more and more frequently. The tumors are benign, and produce no characteristic symptoms. When small they are, therefore, likely to be found only accidentally in operations for other indications. They may, however, reach very large size, in which case they produce discomfort or pain, with perhaps the presence of a mass noticeable to the patient herself. The pathologic characteristics have been described in the paper. The essential elements are (1) the presence of nests or columns, often partially cystic, of rather uniform size and appearance embedded in (2) a matrix of fibromatous tissue which is sharply marked off from the surrounding ovarian stroma though there is no definite capsule. The tumors probably arise from the so-called Walthard islands of indifferent cells which may at times occur in the ovary, though other explanations have been suggested.

The most interesting histologic characteristic is the frequently observed transition of the cells into a cylindrical type identical with that characterizing the ordinary pseudomucinous cystadenoma, so that large tumors of the latter variety may be produced, with only small nodular Brenner tumor vestiges in the wall to indicate their origin. There is logic, therefore, in the subdivision of Brenner tumors into the solid and cystic varieties. Three such tumors are included in our series. On the other hand the fibromatous reaction may be so striking as to produce large fibromas of the ovary. In such cases, of which 2 are included in our group of cases, the origin is indicated by the finding of the typical cell nests scattered either sparsely or richly throughout the tumor. There is little or no evidence to indicate that Brenner tumors exert any such endocrine effects upon sex characters as those which characterize granulosa cell carcinoma or arrhenoblastoma.

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greatest diameter, and on section seemed to be a fibroma. On microscopic examination, however, it showed numerous scattered epithelial cell nests, many with central degeneration, and some showing the typical ovumlike appearance of the central protoplasmic mass (Fig. 12). As the uterus was not removed, the endometrium was not available for study.

CASE 11.—(Gyn. Path. 12512.) This patient was 62 years old, and entered the hospital because of great abdominal enlargement and also vaginal bleeding. She had menstruated normally until the age of 22, when menstruation ceased completely, presumably a precocious menopause of endocrinopathic causation. At the age of 60 she began to have bleeding irregularly and scantily, this continuing for six months, followed by cessation for six months, and then reappearance of the bleeding, which had persisted up to the time of admission. The abdominal enlargement was found to be due to a large ovarian cyst, and left salpingo-oophorectomy was done. The right adnexa and the uterus were not removed, being normal in appearance.

The left ovarian tumor measured 21 by 19 by 18½ cm. and microscopic examination showed it to be a benign, multilocular, pseudomucinous cystadenoma. In several areas, however, the wall showed firm, fibrous solid areas, and microscopic examination of these showed the typical picture of Brenner tumors. Most interesting, however, was the gradual transition of these areas into the cystadenoma. In places, the Brenner islands were solid, in others cystic, and in the latter the inner layer was seen to have become tall, columnar, and pseudomucinous (Fig. 10). Gradually the pseudomucinous epithelium dominated the entire picture, producing the characteristic pattern of pseudomucinous cystadenoma.

CASE 12.—(Gyn. Path. 9157.) The patient, aged 63 years, entered the hospital complaining of an abdominal mass and of lower abdominal pain. She had had a large ovarian tumor, presumably a cyst, removed at the age of 24, and she had had a normal menopause shortly after the birth of her last child, at the age of 42. There had been no bleeding since then. The tumor in this case proved to be a large pseudomucinous cyst of the remaining ovary, and this was removed, with the tube. In the walls there was found a solid area which, under the microscope, revealed the typical picture of a Brenner tumor. Here, as in Case 11, one found a gradual transition to and then replacement by the characteristic epithelium of the pseudomucinous cystadenoma. An interesting feature in the Brenner areas was that even some rather large cystic cavities showed a lining of stratified epithelium, with transition to pseudomucinous epithelium.

CASE 13.—This specimen was recently sent to one of us (E. N.) by Dr. E. S. Edlow, of Sinai Hospital, Baltimore, to whom we are indebted also for the clinical data on the case. The patient was a nulliparous white woman of 27, who entered the hospital on Dec. 7, 1938, with a history of amenorrhea from October 6 until two weeks before admission, when vaginal spotting appeared, continuing up to the time of admission. The cervix was rather soft, the uterus somewhat enlarged, the left adnexa negative, but in the right adnexal region there was a fusiform swelling about 1½ cm. in diameter. A presumptive diagnosis of right tubal pregnancy was made, but operation revealed the right-sided swelling to be due to an enlargement of the ovary by a small fibromalike tumor located cortically. As it was thought to be benign, only the tumor-bearing segment of the ovary was resected. Curettage was then performed, revealing what was apparently decidua tissue, and this was confirmed by microscopic examination. The histologic examination of the small ovarian tumor showed it to be a typical solid Brenner tumor.

CASE 14.—For the slide and data concerning this case we are indebted to Dr. George L. Streeter and Dr. Elizabeth Ramsay, of the Carnegie Institute of Embryology. The patient was 35 years old, and she had had previous pregnancies, 5 terminating in abortion, and 1 in premature stillbirth at the seventh month. She was thought to be pregnant again at about one and one-half to two months, when slight vaginal bleeding appeared, persisting for two weeks, when it became much freer. Two days later laparotomy was done, possibly under the suspicion of tubal

Uneventful convalescence followed, with regression of the malignant growth and no apparent recurrence during an observation period of ten years.

The patient was readmitted Sept. 14, 1935, because of a gradual enlargement of the abdomen of four months' duration. Examination showed the cervix to be almost obliterated with moderate contracture of the vaginal vault. The uterus was

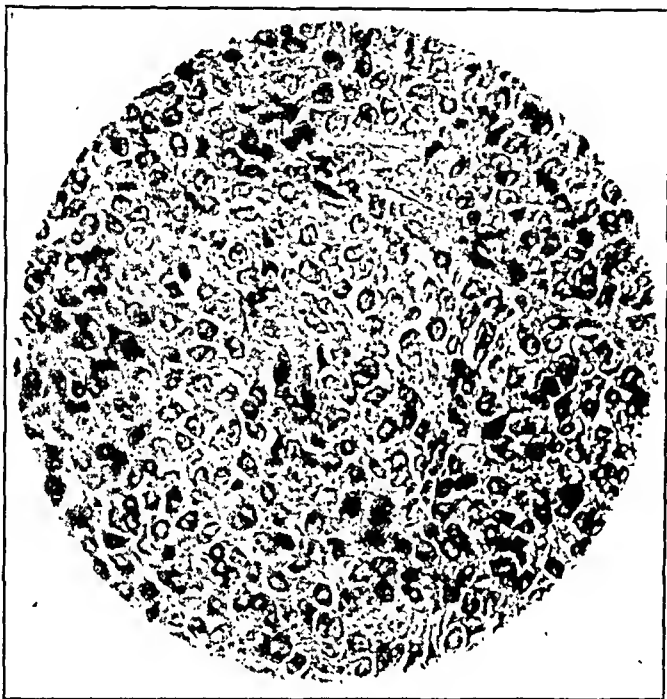


Fig. 1.—Granulosa cell tumor of ovary. High power ( $\times 250$ ).

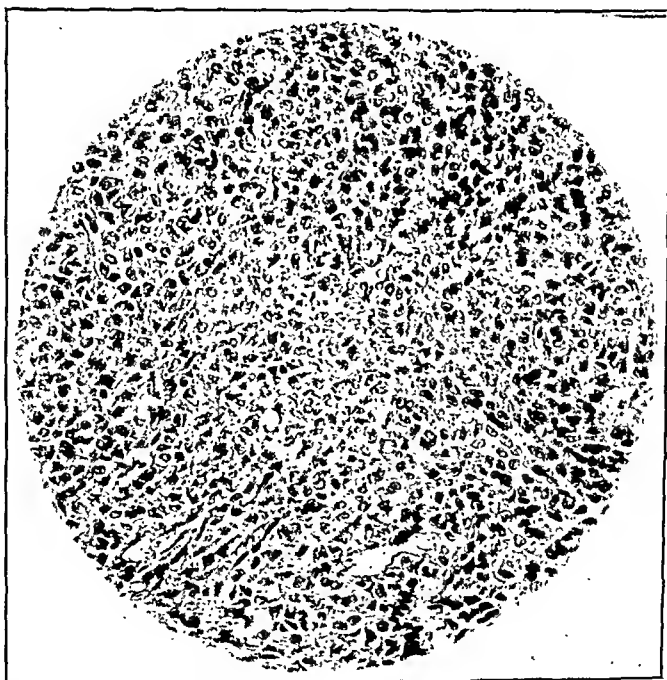


Fig. 2.—Granulosa cell tumor of ovary. High power ( $\times 250$ ).

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## DISCUSSION

DR. WILLIAM C. DANFORTH, EVANSTON, ILL.—I am particularly interested in Novak's explanation of the histogenesis of the Brenner tumor. That the islands of Walthard provide the starting point of these growths seems to be the most widely accepted theory. The essayist suggests the possibility of metaplasia of the germinal epithelium or peritoneum as mechanism for the production of nests of cells which at least resemble the Walthard islands and which may be the point of origin. The explanation of Schiller, that these tumors arise from inclusions in the ovary of epithelium from the embryonic urogenital system, seems less convincing. A third theory, not mentioned by the essayist, that these tumors are to be regarded as a one-sided type of teratoma because of their occasional association with pseudomucinous cystadenomas does not seem to me to be applicable as only a minority of these growths are accompanied by such cystadenomas.

The clinically benign character of these tumors seems quite definitely established and operation need go no further than the excision of the tumor and such other surgery as may seem clearly indicated.

The tremendous variation in size of these tumors was brought out by Novak. In our much smaller series the growths vary from an enormous cystadenoma to a microscopic tumor which was unrecognized on the operating table or in the laboratory on gross examination and was only found on routine section of the ovary.

I will give a brief report of the three cases which have occurred in our own work.

The first was a woman of 45 years, a ward case, already reported by Philip H. Smith. In the right ovary, there was a solid tumor about the size of a hen's egg which proved to be a Brenner tumor of the solid type, containing a number of small epithelial cell nests in some of which are seen the typical vacuoles.

The second case, a woman of 51 years, was a private patient of H. J. Holloway. A large pseudomucinous cyst was found 22 by 10 by 8 cm., containing about 1,000 c.c. of fluid. In the hilum was a solid mass in which were present the usual cell nests characteristic of the Brenner tumor but with a greater amount of mucinous material than the preceding case.

The third case was a patient of my own, a woman of 68 years, who was operated upon for a very early carcinoma of the corpus uteri. Both ovaries appeared entirely normal upon the operating table, and the pathologist noted nothing abnormal about them upon gross examination. Upon routine section small cell nests with the characteristic vacuoles were found. These were much smaller than in the preceding cases, most of the nests not being over 1 mm. in diameter.

DR. LEWIS C. SCHEFFEY, PHILADELPHIA, PA.—I wish to record two interesting and curious cases that have come to our attention on the Gynecologic Ward Service at Jefferson Medical College Hospital. They are interesting because they deal with the development of granulosa cell tumors of the ovary in patients previously treated successfully with radium for carcinoma of the cervix.

CASE 1.—The first patient was a white woman of 54, para x, admitted Oct. 26, 1925. She had developed a bloody vaginal discharge for three months previously, and six years after her menopause. A diagnosis of carcinoma of the cervix, intermediate grade of malignancy (Group III, Schmitz), was made by biopsy and application was made of 150 mg. of radium for twenty-four hours.

sisted of ovarian stroma in which corpora albicantes were seen. The tumor proper was composed of many compartments which were composed of granulosalike cells which were arranged in folliclelike formations (Fig. 2).

Diagnosis: Granulosa cell tumor of the ovary.

Convalescence has been uneventful.

DR. GRETA STOHR, NEW YORK, N. Y. (by invitation).—Among 9 cases of tumor ovarii Brenner at the Woman's Hospital, New York, we observed one case which seems to support the theory that these rare tumors might take their origin in the rete ovarii. Similar findings, but none as determinative as the one to be presented, are those described by Schiller and Fauvet. The case represents an accidental finding, since the whole tumor did not exceed a diameter of about 3 mm. It was seated in the hilus of an ovary which was essentially of normal type.

Microscopically we found a peculiar topographical relationship between the rete and the small tumor. The latter, which is a well circumscribed body, composed of the characteristic epithelial nests and the connective tissue stroma, is densely adjacent to the well-developed rete and there is an intimate interweaving of rete ducts and the nests of Brenner epithelium. In detail photographs rete tubules are found in several instances within or on the periphery of Brenner epithelial inclusions. Here seemingly a transition of the simple low cuboidal epithelium into the undifferentiated pavement epithelium has taken place. The production of mucus is apparent in one cystic structure, which is lined partly by Brenner epithelium and partly by the low cuboidal epithelium of the rete tubule. The lumen of the space is filled with a substance, which gives a positive mucicarmin reaction.

Since both types of epithelium take part in the lining of the small cystic space, the exact origin of the mucous matter is not evident. This fact might be better elucidated by the following slide, which reveals a typical tubule of the rete distended by mucous content without the evidence of a morphologic alteration of the epithelium proper. Such structures, therefore, might be considered as indicative of a biologic functional transformation of the tubular epithelium correlated with its morphologic transformation, and as an initial process conducive ultimately to heterotopic tumor formation.

DR. NOVAK (closing).—As I mentioned in my paper, no one can speak with assurance as to the histogenesis of Brenner tumors, and it is quite possible that there is more than one source. For reasons which I have already discussed, the Walthard islands seem to me important, especially since all degrees of transition can be demonstrated between these and the fully formed Brenner tumors.

From a laboratory standpoint one may urge the importance of searching for evidences of Brenner tumor in the walls of cystadenomas and in the structure of fibromas. The microscopic appearance of Brenner tumors is really quite distinctive, so that, once pathologists become familiar with this tumor type, diagnosis will be easy, and the tumor will be found to be not nearly so rare as the present number of reported cases would seem to indicate.

of normal size and position but with lessened mobility. A cystic mass, about the size of a honeydew melon, could be palpated as a freely movable enlargement low in the pelvis. With a preoperative diagnosis of ovarian cyst, I operated upon her on Sept. 19, 1935. Abdominal section revealed a multilocular ovarian tumor, springing from the left adnexal region with a partial twist of the pedicle. The right tube and ovary were normal. The uterine fundus was small, atrophic, and movable. There was no induration of the broad ligaments, and no evidence of carcinomatous areas anywhere in the abdomen. A small amount of brownish fluid was present in the peritoneal cavity. Left salpingo-oophorectomy was performed. The vaginal biopsy showed hyalinized tissue, while the ovarian tumor was described by B. L. Crawford and Hoffman as follows:

Specimen consisted of an oval-shaped cystic and solid tumor which weighed 2,000 gm. and measured 22 by 16 by 14 cm. The cystic portion measured 16 cm. in diameter and was covered by a thin smooth glistening membrane. The solid portion was nodular in shape and measured 10 by 6 by 6 cm. The cyst was unilocular in nature and contained a clear amber-colored serous fluid. The interior of the cyst wall was perfectly smooth. The solid portion on section revealed a friable soft yellowish gray tissue in which many small cystic areas were noted. Some of these cystic areas were filled with a necrotic blood or yellowish gray tissue having the consistency of brain tissue.

The cystic portion was lined by a thin fibrous connective tissue capsule which was partly lined by low cuboidal epithelial cells. The solid portions of the tumor were composed of a very cellular tumor growth. The individual cells resembled the normal granulosa cells of the follicles. In many locations these cells were so grouped as to give the impression of numerous small primordial follicle formations. In some locations these cells presented gyrate formations. A few corpora albicantes were likewise noted (Fig. 1).

Diagnosis: Granulosa cell tumor of the ovary.

This patient has since been seen at regular intervals and has remained well.

CASE 2.—R. D. was a white woman, para iv, admitted on Sept. 14, 1930. She had had three previous operations, an appendectomy, 1910; a cholecystostomy, 1911; and a possible supravaginal hysterectomy with unilateral salpingo-oophorectomy, 1912. No written verification of this last operation was obtained, but there had been no menstruation following it during a period of eighteen years. Vaginal bleeding ("spotting") had occurred intermittently for two years prior to admission at which time a diagnosis of squamous cell carcinoma of the cervix, low grade (Group III, Schmitz) was made. Application was made of 150 mg. of radium for twenty-four hours. Convalescence was uneventful and the patient showed no recurrence of the cervical carcinoma during an observation period of eight years.

The patient was readmitted April 22, 1939, with a history of an enlargement of the lower abdomen of about nine months' duration. Pelvic examination showed an atrophic contracted vaginal vault with some semblance of an external cervical os. Parametrial fixation was present, together with a pelvic mass the size of a four months' pregnancy, which was thought to be an enlarged fundus, probably adherent to a loop of bowel. The preoperative diagnosis was fibroma uteri with intestinal and pelvic adhesions. Abdominal section (May 2, 1939) revealed a cystic tumor, the size of a honeydew melon, which had the appearance of a parovarian cyst, arising from the pelvis. The right uterine tube was attached and spread out over the surface of the tumor, which was semisolid and cystic, being diffusely adherent to the omentum, small intestine and parietal peritoneum. There was no evidence of a uterine fundus or left adnexa. The tumor was mobilized with some difficulty, and the capsule ruptured just before its removal at a point adherent to the rectal wall. The tumor was described by Drs. B. L. Crawford and J. Hoffman as follows: Specimen consisted of a large ovarian tumor which weighed 1,250 gm. and measured 17 by 14 by 11 cm. The tumor was soft and cystic and was covered by a pinkish red capsule which in some areas was duplicated upon itself. A few adhesions were seen on the surface of the tumor. The capsule of the tumor was intact and con-



The left ureter had perforated spontaneously into the peritoneal cavity, and there were urinary ascites and chronic peritonitis. The patient succumbed and careful autopsy failed to reveal any remaining carcinoma. Again in 1933, I<sup>6</sup> reported 18 cases showing urinary tract complications following pelvic irradiation. Seven of these 18 patients were suffering from vesicovaginal fistula, and 6 of these 7 were proved to have dense strictures of the lower ureters. The other 11 patients all had very dense strictures of both ureters with resulting upper tract damage. Three of these patients had received irradiation for benign lesions, and of the other 15 in whom the treatment had been administered for carcinoma, all but 2, so far as could be determined, were free from carcinoma at the time they presented themselves because of the urologic condition. The absence of urinary tract symptoms previous to irradiation in most of these patients suggested that the conditions found had developed as a result of the therapy, and of course in the cases with fistula no doubt of this fact can be entertained. In our experience, however, it is not unusual to find patients with ureteral strictures and moderate degrees of hydronephrosis who present very few or no localizing symptoms. It is therefore not a wholly justifiable contention that the damage to the upper tracts found in these cases was due entirely to the irradiation. The possibility must be considered that such lesions may have existed previous to irradiation and that they may merely have been increased to the point of producing symptoms by the lapse of time, and especially, as a result of this type of therapy. It was in an attempt to throw further light upon this question that the present study was undertaken.

In planning the study it was hoped that satisfactory answers to the following questions might be found:

1. What types of complications are found in the bladder as a result of irradiation, and with what frequency do they occur?
2. At what stage in its progress does carcinoma begin to encroach upon and occlude the ureters?
3. Does irradiation therapy ever cause a regression and alleviation of such ureteral damage?
4. Does irradiation therapy per se ever result in ureteral damage with stricture formation and upper tract dilatation?

In an attempt to answer these questions 46 patients have been subjected to urologic study before any treatment was administered. Thirty-three patients have been similarly studied from three months to five years after the administration of irradiation therapy. Of these 33 patients, 17 were taken from the group of 46 who had been studied before treatment, while in 16 others such preliminary study had not been carried out. In all of these patients the carcinoma as far as could be determined was either cured or entirely quiescent at the time of study and further follow-up examinations, as recently as time has permitted, show that they have remained so.

# THE EFFECT OF CARCINOMA OF THE CERVIX UTERI AND ITS TREATMENT UPON THE URINARY TRACT\*

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ALTHOUGH the destructive effects upon the urinary tract of untreated and uncontrolled carcinoma of the cervix uteri has been long widely recognized, in recent years a renewed interest has been shown in this subject because of the possible alteration in the course of the disease resulting from its treatment by irradiation. Careful autopsy studies along these lines have been reported by Behney,<sup>1</sup> Faerber,<sup>2</sup> Morton,<sup>3</sup> and Herger and Schreiner.<sup>4</sup> The first three of these articles deal with general considerations as to the alteration of the progress of the disease as a result of irradiation therapy, but the articles of Behney and Morton are of considerable importance because they each record three cases in which death followed very rapidly upon irradiation and could be directly attributed to the treatment. In the three cases recorded by Behney death was due to a massive necrosis and sloughing of the pelvic tissues and in two of these autopsies failed to reveal any remaining carcinoma, thus suggesting the possibility that irradiation therapy may at times cause serious destruction of normal tissues.

The study of autopsy material is always of great value in throwing light upon the course and eventual termination of a disease entity. In the reports mentioned, however, the vast majority of the patients studied had succumbed to the carcinoma. To the clinician and therapist it is of far greater importance to know what types of complications may arise as a result of treatment in those patients in whom the highly desired effect of completely eradicating the cancerous process is achieved. Armed with such knowledge the clinician then may attempt to alter the treatment in such a way as to avoid the complications, or finding this impossible, he may add to his therapeutic procedures such measures as may tend to ward off such complications, or alleviate them once they have already arisen. These principles are particularly applicable to complications arising in the urinary tract in patients treated for cervical carcinoma by irradiation.

My interest in this subject was first aroused in 1929, when Dr. Guy L. Hunner and I<sup>5</sup> encountered and reported the case of a patient who, eighteen months after successful treatment for carcinoma of the cervix by radium and deep x-ray, presented herself with a vesicovaginal fistula, dense strictures in the lower ends of both ureters, bilateral infected hydroureter and hydronephrosis, and bilateral pyelonephritis.

\*Read, by invitation, at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1930.

A summary of some of the reports of this type of lesion as gathered from the literature is presented in Table I. In view of the relatively small dosage of irradiation that had been given some of these patients, Dean suggested the probability of individual susceptibility of the bladder tissues to such injury. Most of the authors are agreed that unless fistulas develop the ulcers eventually tend to heal, but that the healing process is a slow one. Various types of treatment have been suggested from simple irrigations to fulguration of the ulcer base, but all are agreed that a most important item is the avoidance of further irradiation, a procedure which may well be suggested and carried out unless the lesions are carefully differentiated by biopsy from carcinomatous invasion.

The effects of irradiation upon the bladder as derived from the present study are shown in Tables II, III, and IV. None of the 46 patients studied before treatment showed evidence of carcinomatous invasion of the bladder. In 7 patients, 2 with Stage I carcinoma, and 5 with Stage III of the disease, the bladder mucosa appeared reddened or injected before treatment. In 3 of these, 1 with Stage I, and 2 with Stage III carcinoma, the urine was infected.

TABLE I. SUMMARY OF CASES OF LATE ULCERATIONS OF THE BLADDER GATHERED FROM THE LITERATURE

AUTHOR AND REFERENCE	YEAR	NO. OF CASES	PER CENT OF PATIENTS TREATED	DEVELOPED FISTULAS	TIME BETWEEN TREATMENT AND APPEARANCE OF LESION	TYPE AND DOSAGE OF IRRADIATION
Dean <sup>9</sup>	1927	3		0	14.5-24 mo.	3272 mc. hr.-6694 mc. hr.
Dean <sup>10</sup>	1933	37	About 2.5 7.3 in recurrent cases	Not stated	1-10 yr. Average 2.5 yr.	1.5 to 8 s.e.d. to base of bladder. Average 5 s.e.d.
Newell and Crossen <sup>11</sup>	1935	4	1+	Not stated	2.5-6 yr.	Not stated
Smith <sup>12</sup>	1932	7		2	11 mo. to 6 yr.	2625 mc. hr.-6288 mc. hr. Average 3500 mc. hr. of screened radon
Colby <sup>13</sup>	1933	12	34.3 of cases studied	7	18 mo. to 6 yr.	Most frequent occurrence followed multiple treatment. Four of 9 cases (44%) developed vesicovaginal fistulas.

TABLE II. SUMMARY OF EFFECT UPON THE URINARY BLADDER OF IRRADIATION OF THE CERVIX

ORIGINAL STAGE OF CARCINOMA		I	II	III	TOTAL
Number of cases studied		14	8	11	33
Bladder mucosa reddened with or without edema	No.	2	2	0	4
	Per cent	14.3	25	0	12.1
Bladder mucosa abnormally pale with or without scarring	No.	2	3	2	7
	Per cent	14.3	37.5	18.2	21.2
Ulceration of bladder	No.	1	2	3	6
	Per cent	7.1	25	27.2	18.2
Vesicovaginal fistula	No.	0	1	0	1
	Per cent	0	12.5	0	3

The study was begun in 1933 but has been interrupted from time to time due to unavoidable circumstances. During the periods that the work has been in progress, however, the patients have been unselected so far as any influence the presence or absence of urinary symptoms may have exerted. Patients with obviously hopeless Stage IV carcinoma have not been accepted for the preliminary studies, and although a few patients have been studied after treatment in whom there was evidence that the carcinoma had not been arrested, these have not been included in the report, as our primary interest has been in the cured patients.

At the beginning of the study the upper tracts were examined by means of ureteral catheterization and retrograde pyelograms. It was found however that the painful reactions which often followed these procedures made it difficult to induce many of the patients to return for the later examinations. More recently therefore intravenous urography\* has been largely used to study the upper tracts, and the more painful procedure of retrograde pyelography has been used in only those cases in which the intravenous method proved unsatisfactory.

With one exception the irradiation therapy has been administered under the direction of Dr. Curtis F. Burnam and his associates at the Howard A. Kelly Hospital, and it is a pleasure to have this opportunity of expressing my thanks for their helpful cooperation.

#### I. EFFECT UPON THE BLADDER

This phase of the subject has been more thoroughly and adequately studied and reported by others than have the other questions which this report attempts to answer. Aman-Jean<sup>7</sup> in France, and Graves, Kieckham, and Nathanson<sup>8</sup> in this country, have stressed the importance of cystoscopic examination of the bladder, before, during, and after treatment as an aid to the evaluation of prognosis, the progress of the disease, and the success or failure of treatment. The latter authors gave the incidence of vesicovaginal fistulas as 62 out of 683 patients studied and of late radiation reaction with ulceration, as 12 out of the same series. It is not made clear, however, how many of these lesions occurred in cured patients, although for the fistulas it is stated that 7 such lesions were found in 226 patients still living.

Dean<sup>9, 10</sup> has made a notable contribution to this subject in reporting and accurately describing late ulcerative lesions occurring in the bladder following irradiation of the uterus. He described three types of reaction to irradiation found in the bladder as follows:

1. Primary erythema occurring within twenty-four hours after treatment and being merely a nonspecific reaction to local irritation.

2. Secondary erythema appearing usually about twenty-eight days after treatment and being a specific reaction to irradiation, probably due to temporary vasodilatation.

3. Tertiary reaction consisting of obliterative endarteritis with sloughing and ulceration of the tissues. These lesions are often covered with grayish slough or gritty deposits and can only be definitely distinguished from carcinomatous invasion by biopsy. They rarely appear earlier than a year and may appear as late as ten years after treatment with an average of two and one-half years.

\*The intravenous urography has been done in most instances with 30 c.c. of diodrast very generously furnished by the Winthrop Chemical Company.

TABLE III. INDIVIDUAL RECORDS OF PATIENTS SHOWING MINOR BLADDER REACTIONS FOLLOWING IRRADIATION

CASE	AGE	ORIGINAL STAGE OF CARCINOMA	DOSAGE OF IRRADIATION		TIME BETWEEN TREATMENT AND REACTION	REACTION		BLADDER SYMPTOMS	URINE			UPPER TRACT LESIONS
			RADIUM IN MC. HR.	X-RAY IN R. UNITS		DESCRIPTION	TYPE AFTER DEAN <sup>10</sup>		CULTURE	PUS	BLOOD	
U 52299	60	I Stump	2500 i & c*	0	42 mo.	Trigone and base very pale	Mild tertiary	0	0	0	0	0
73250	31	I	1410	0	10 mo.	Trigone reddened	Secondary?	0	0	0	+	0
U 43971	36	I	2100 c 1300 i	0	26 mo.	Pallor and scarring of rt. base and trigone	Mild tertiary	+	0	tr.	tr.	Occlusion of right ureter with functionless kidney. Fig. 1
137399	41	I	1500 c 1600 i	11,760 re-treatment after 36 mo.	41 mo. 5 mo.	Localized reddening and edema 4 cm. in diameter rt. base. Healed after two months	Secondary to x-ray	+	B. coh	+	0	0
149543	55	II	450 c 2649 i	8400	3 mo. 6 mo.	Red, edematous trigone Trigone and base scarred	Secondary Tertiary mild	+	0	tr.	tr.	Moderate dilatation left ureter. Fig. 2
149704	59	II	2540 i & c	12,180	5 mo.	Base pale with transverse ridges	Mild tertiary	+	0	tr.	tr.	0
U 10901	33	II	2965 i & c	0	6 mo.	Edema and reddening of trigone	Secondary, or cystitis	+++	B. coh	+	0	Moderate bilateral dilatation
135255	64	II	Retreatment after 25 mo. 2400 i & c	10,340	34 mo. 9 mo.	Trigone and base pale and rigid	Mild tertiary	0	0	0	0	0

\*c, Contracervical; i, intracervical.

The incidence of late bladder ulcerations in this series, 18 per cent, is considerably higher than in most series previously reported, but this is easily accounted for by the fact that our percentage is calculated on the basis of cured patients actually studied, while most of the other authors have used the total number of patients treated during the period of study as a basis of calculation. As compared with Colby whose percentage is calculated in the same way as ours, our figure is considerably lower.

The reactions described in Table III are perhaps of no great significance as in most instances they were producing no symptoms. They are presented, however, with the thought that they may possibly suggest the way in which the more serious later lesions develop. Cases 149543 and 110917, for instance, at an early study presented



Fig. 1.



Fig. 2.

Fig. 1.—(Case U 43971.) Twelve-minute intravenous pyelogram twenty-six months after 2,100 mc. hr. of radium contracervical and 1,300 mc. hr. intracervical for Stage I carcinoma of the cervix. Note the unusual density of the shadow of the right kidney, but the absence of excretion of the opaque material on this side. The right ureter could not be catheterized due to dense scarring of the right side of the trigone involving the lower ureter, and 40 per cent phenolsulphonephthalein was excreted by the left kidney in a half hour.

Fig. 2.—(Case 149543.) Original Stage II carcinoma complicated by a small uterine fibroid. Left pyeloureterogram made six months after 3,109 mc. hr. of radium emanations and 8,400 r. of deep x-ray therapy. Note moderate dilatation of the ureter and pelvis. Intravenous urograms taken before treatment showed normal tracts, but unfortunately due to marked obesity of the patient the visualization in those plates is not sufficient to permit satisfactory reproductions.

the appearance of erythema, or the secondary reaction of Dean, although in both instances this reaction appeared somewhat later than the twenty-eight days after treatment suggested by that author. Both these patients at later studies showed marked pallor and thickening of the trigone and base, which may be interpreted, it seems, as caused by a mild ischemia resulting from obliterative endarteritis. Such obliterative endarteritis, in severer forms, is generally believed to be the cause of ulceration and fistula formation. Indeed Case 110917 eventually developed multiple ulcerations of the bladder base twenty-two months after treatment. A further confirmation of this idea is afforded by the patient in Case K 83527 who when studied in July, 1937, thirteen months after 3788 mc. hours of radium emanations applied against the cervix and in the canal, showed extreme pallor of the base of the bladder with scattered areas of petechial reddening. This patient returned in March, 1939, thirty-three months after treatment with gross

TABLE IV. INDIVIDUAL RECORDS OF PATIENTS SHOWING LATE, MORE SERIOUS BLADDER REACTIONS FOLLOWING IRRADIATION

CASE	AGE	ORIGINAL STAGE OF CARCINOMA	DOSAGE OF IRRADIATION		TIME BETWEEN TREATMENT AND LESION	DESCRIPTION OF LESION	BLADDER SYMPTOMS	URINE			UPPER TRACT LESIONS
			RADIUM IN MC. HR.	X-RAY IN R. UNITS				CULTURE	PUS	BLOOD	
100368	28	I	2000 c* 1000 i	0	24 mo.	Necrotic ulceration in rt. base which healed spontaneously	+++	0	+	+	Not determined
K 97218	35	II	2800 i & c	12,420 over 2 mo. Later 13,500 over 2½ mo. over 2½ mo.	10 mo. from radium. 2½ mo. from x-ray 14 mo. later	Trigone pale, scarred on left side  Vesicovaginal fistula	+	0	0	0	Left ureter obstructed
K 80924	50	II Stump	2530 c	0	7 mo. 14 & 17 mo.	Small ulcerations in base Healed, bladder normal	+	0	0	+	0
K 83527	57	III	2185 c 1603 i	0	13 mo. 32 mo.	Mucosa very pale with petechial reddening Tertiary ulceration of bladder base	0	0	0	+	0
127093	58	III	2600 c	0	21 mo.	Extensive ulceration of trigone, base, and vesical neck with calcium phosphate encrustations	+++	Mixed	++++	++	Marked bilateral dilatation. Fig. 5
155849	27	III Adeno-carcinoma	2040 i re-treatment after 19 mo.	11,895 0	8 mo. 2 mo.	Ulcerations and necrosis in base and anterior wall—healed in 3 mo. Recurrence of ulcer in base	++ ++	0 0	++ +	++ +	0 0

\*c, Contracervical; i, intracervical.

110917	57	II	2870 i & c	11,960 re-treatment after 6 mo.	12 mo. after radium	Diffuse reddening entire bladder	Secondary	+++	0	++	0	Moderate bilateral dilatation. Fig. 3
					20 mo. after radium	Base and trigone very pale with red patches	Mild tertiary†	0	0	0	tr.	
K 5814	54	III	1500 i 1500 c 2 gold points in each parametrium		60 mo.	Trigone thickened and edematous, granulations around right orifice	Mild tertiary	++ After x-ray	0	0	0	Moderate bilateral dilatation
			Retreatment after 30 mo. 1600 c		30 mo.							
				8640 re-treatment after 72 mo.	4 mo.							

†This patient developed multiple ulcerations of the base of the bladder twenty-two months after treatment.



of the disease. In the 28 patients classified by means of vaginal and rectal examination as having Stage III carcinoma, 16, or 57.1 per cent, showed evidence of upper tract damage (Figs. 6, 7, and 8). There has been no evidence of cure or control of the carcinoma in any of these patients, and naturally therefore, no evidence of regression of the ureteral and upper tract lesions. The most interesting group is that comprised by those 12 patients classified by the ordinary clinical methods as having Stage III carcinoma, but who showed no evidence of encroachment upon the ureters. Nine, or 75 per cent, of these patients have survived, and the course of some of them suggests that the induration and fixation felt in the parametrial regions at the time of the original examination may have been due to an associated inflammatory process, rather than to actual extension of the carcinoma. The following case report affords a striking example of this observation.

TABLE V. THE PROGNOSTIC SIGNIFICANCE OF UPPER URINARY TRACT DAMAGE BEFORE TREATMENT

STAGE OF CARCINOMA	NO. OF CASES STUDIED	NO. WITH UPPER TRACT DAMAGE	NO. WITHOUT UPPER TRACT DAMAGE	RESULT OF TREATMENT
I	9	0		
			9	All patients living and apparently well 5 months to 5 years after treatment
II	9	0		
			9	2 died 6 months after treatment. 7 apparently cured
III	28	16		9 died 6 hopeless 1 still under treatment
			12	9 apparently well 1 dead 2 still under treatment

E. M. (Case 118896), white, aged 35 years, was seen first July 28, 1937, complaining of slight vaginal bleeding for seven months. She had undergone a supravaginal hysterectomy in 1924, and had had no bleeding since that time until January, 1937. Examination showed a carcinoma involving the whole of the cervix and extending on to the anterior vaginal wall, with induration in both parametrial regions. The patient had suffered from slight frequency and nocturia but no dysuria. The urinary tract was studied on Aug. 11 and 19, 1937. These studies showed a mild injection of the bladder mucosa and some trabeculation of the base and fundus. There was only an occasional pus cell in the urine, but cultures from the bladder and both kidneys were positive for *Bacillus coli*. The function of both kidneys as determined by the phenolsulphonephthalein excretion was excellent. Retrograde pyeloureterograms of both tracts showed normal findings (Fig. 9). From Aug. 11 to Sept. 10, 1937, the patient received 5,940 R.U. of deep x-ray therapy, and on Aug. 2, 1295 mc. hr. of radium emanations were applied against the cervix and on Sept. 4, 1154 mc. hr. in the cervical canal. The patient appeared to respond poorly. Although the local growth disappeared and the involved areas healed, the induration in the parametria persisted and the patient felt weak and chronically ill.

On Jan. 10, 1938, because of a persistence of bladder symptoms, she was again cystoscoped, but upon this examination the bladder appeared normal and the urine was sterile. In the late Spring of 1938, she began to improve symptomatically

hemorrhage from an extensive ulcerative lesion of the bladder base. A month previous to this last episode she had been entirely free of urinary symptoms. There is absolutely no evidence of remaining carcinoma.

Tables III and IV suggest the role of retreatment in the production of bladder lesions, 4 of the 10 patients with mild reactions, and 2 of the 6 patients with severer lesions having been retreated. None of the 5 patients with bladder ulceration had had more than very moderate dosage of irradiation, suggesting the possibility of individual susceptibility to such a reaction. This is particularly emphasized by Case 155849 who developed extensive bladder ulceration eight months after

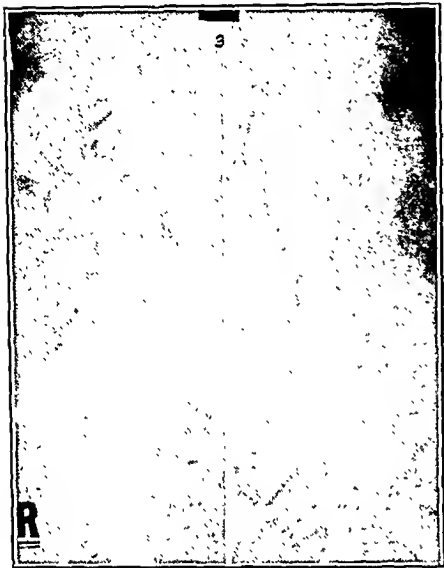


Fig. 3.



Fig. 4.

Fig. 3.—(Case 110917.) Original Stage II carcinoma. Right and left pyelograms twenty months after original treatment of 2,870 mc. hr. of radium emanations intra- and contracervical, and fourteen months after a retreatment of 11,960 r. of x-ray. At the time of this examination the trigone and base of the bladder showed marked pallor with petechial areas of reddening. Despite the marked bilateral hydronephrosis and hydroureter, the function of these kidneys was unimpaired.

Fig. 4.—(Case 97218.) Right pyeloureterogram twenty-four months after initial treatment of 2,800 mc. hr. of radium emanations for Stage II carcinoma. In addition the patient had been given two courses of deep x-ray therapy, one of 12,420 r. and one of 13,500 r. At the time of this examination she appeared to be well of carcinoma, but had developed a vesicovaginal fistula with complete occlusion of the left ureter and functionless left kidney.

completion of a course of 11,895 r. units of x-ray. This lesion healed but reappeared twenty-one months later, two months after the application of 1,040 mc. hr. of radium emanations. The association of upper tract lesions with the bladder reaction in 7 of these 16 patients suggests that scarring of the bladder wall involving the intravesical portions of the ureters may frequently account for the upper tract damage encountered. The failure to obtain positive bacterial cultures from the urine in most of the cases, even in the presence of blood and pus and actual ulceration, is further evidence that these findings are true reactions on the part of the vesical tissues to the irradiation, and not the result of urinary infection.

## II. THE PROGNOSTIC VALUE OF STUDYING THE UPPER URINARY TRACTS BEFORE TREATMENT

Table V shows the results of study of the upper urinary tracts in 46 patients before any treatment was instituted. As was to be expected there is no evidence of any encroachment upon the ureters in patients suffering from Stages I and II

and when she was again studied on July 28, was feeling quite well. Examination at this time, however, showed persistence of induration in the broad ligaments, much scarring of the vaginal vault, and some ulceration at the original site of the tumor. The urine was again sterile and intravenous pyelograms showed rapid excretion and perfectly normal pelvis, calyces, and ureters (Fig. 10). Re-examination on Jan. 6, 1939, showed the patient feeling quite well, and that all the pelvic tissues had healed, and the parametrial induration had entirely disappeared.

From the ultimate outcome in this case it would seem that the patient's long chronic illness was probably due to an associated inflammatory process and not to progressing carcinoma, and it seems probable that this should have been suggested by the normal intravenous pyelograms taken on July 28, while massive



Fig. 9.



Fig. 10.

Fig. 9.—(Case 118896.) Left pyeloureterogram made before treatment in a patient diagnosed as Stage III carcinoma because of broad ligament induration. Pyeloureterogram of the right side also showed a normal tract.

Fig. 10.—(Case 118896.) Five-minute intravenous urograms taken eleven months after treatment of the same patient illustrated in Fig. 9. The upper urinary tracts appear normal in spite of the fact that there was still parametrial induration. The patient was improved symptomatically, however, and six months later the pelvic induration was no longer present.

pelvic induration still existed. That pelvic inflammatory disease does not tend to produce ureteral obstruction has been suggested by Kretschmer and Kanter,<sup>14</sup> and is further borne out by the patient whose intravenous pyelograms are shown in Fig. 11. At the time these films were made this patient had been suffering for more than two months from a massive postabortal cellulitis. As can be seen from the x-rays there was a mass in the right side of the pelvis sufficiently large to produce marked medial displacement of the right side of the bladder and lower right ureter, but still there is no evidence of dilatation of the upper ureter or pelvis.

### III. THE EFFECTS OF IRRADIATION THERAPY UPON THE UPPER URINARY TRACTS

A clear analysis of the clinical literature in regard to this phase of the subject is difficult for two reasons, first because no clear differentiation is made by

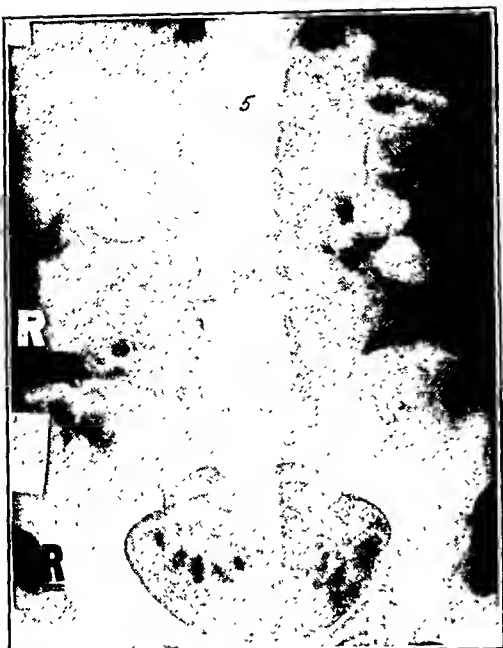


Fig. 5.



Fig. 6.

Fig. 5.—(Case 127093.) Thirty-three-minute intravenous pyelograms made three years after treatment with 2,600 mc. hr. of radium emanations for supposed Stage III carcinoma. At the time of this examination the patient had been suffering for more than a year from an intense ulcerative cystitis with encrustations, but was apparently well of carcinoma. The films taken earlier than thirty-three minutes showed little visualization.

Fig. 6.—(Case 122344.) Stage III carcinoma. Pyeloureterograms made before treatment. Treatment: 3,500 mc. hr. of radium emanations. Patient died seven months after treatment. Autopsy showed extensive carcinoma with vesicovaginal fistula, destruction of lower end of left ureter, bilateral hydronephrosis and left hydro-nephrosis.



Fig. 7.



Fig. 8.

Fig. 7.—(Case K 62444.) Stage III carcinoma. Intravenous urograms before treatment. Six months after treatment patient was in the Baltimore City Hospital with a hopelessly advanced carcinoma. Studies there showed a vesicovaginal fistula, a functionless right kidney, and marked dilatation of the left tract. The patient died eight months after treatment.

Fig. 8.—(Case K 41523.) Stage III carcinoma. Intravenous pyeloureterograms with catheter in left ureter, made before treatment. Treatment: 3,000 mc. hr. of radium emanations. The patient died four and one-half months after treatment.



Fig. 15.



Fig. 16.

Fig. 15.—(Case 146745.) Original Stage III carcinoma. Pyeloureterograms made forty-two months after treatment by irradiation. The patient was apparently well of carcinoma at the time of this examination.

Fig. 16.—(Case 155620.) Stage III carcinoma. Fifteen-minute intravenous urogram made before treatment. There was rapid excretion of the dye and rapid emptying of the upper urinary tracts which appear normal.



Fig. 17.—Thirty-minute intravenous urogram of the same patient illustrated in Fig. 16, made six months after 3,595 mc. hr. of radium emanations applied against the cervix and 10,340 r. units of x-ray. Pelvic and rectal examination at this time showed the cervix healed and all pelvic tissues soft. The plate shows moderate but definite dilatation of both ureters and much slower emptying than was found in the study made before treatment.

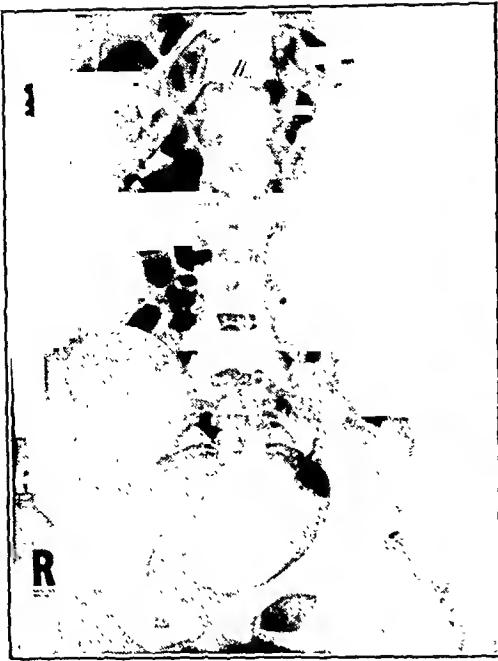


Fig. 11.



Fig. 12.

Fig. 11.—Intravenous urograms of a patient who had been suffering for two months from a postabortal pelvic cellulitis. Note that there is a right-sided pelvic mass sufficiently large to cause marked displacement of the bladder, but that there is no dilatation of the ureters or kidney pelvises.

Fig. 12.—(Case K 96211.) Original Stage I carcinoma. Pyeloureterograms made seven and ten months after 2,700 mc. hr. of radium emanations against the cervix. Patient is still apparently well of carcinoma more than two years since the treatment.



Fig. 13.



Fig. 14.

Fig. 13.—(Case U 10901.) Stage II carcinoma. Bilateral pyeloureterograms six months after 2,965 mc. hr. of radium emanations against the cervix and in the canal. Intravenous pyelograms before treatment showed normal tracts while these show definite but moderate dilatations. The carcinoma was apparently arrested at the time this plate was made.

Fig. 14.—(Case K 5418.) Original Stage III carcinoma. Right pyeloureterogram five and one-half years after first treatment with 4,500 mc. hr. of radium emanations, including gold points in the parametria. Patient had received a retreatment of 1,600 mc. hr. three years after the original treatment and 8,640 r. of x-ray six months before this plate was made. These retreatments were given as precautionary measures and the patient was apparently well at the time of this examination. Note the permanent needle in the right parametrium and note its distance from the ureter.

to no very definite conclusions, as the percentage of patients showing upper tract damage after treatment is slightly less than was found in the group studied before treatment. If the fact is recalled, however, that none of the patients with this advanced stage of the disease, who showed upper tract damage before treatment, have survived sufficiently long to permit of the later studies, the 50 per cent of upper tract damage, found in 11 patients with apparently cured or arrested carcinoma, is seen to be of considerable significance. The figures in regard to patients originally found to have carcinomas in Stages I or II can hardly be open to question, particularly since the figures in the larger group shown in Table VI are fairly closely approximated by the smaller control group shown in Table VII. It would seem therefore that the figure of approximately 50 per cent showing some degree of upper tract damage after irradiation must be very nearly a true estimate of the incidence of such findings.

A study of Table VIII discloses that in 10 of the patients with evidence of upper tract damage, this damage was very moderate, but in 5 of these 10 the studies were made less than a year following irradiation; while in 4 of the 5 patients showing severe lesions, the studies were made from twenty to forty-two months following treatment. It would seem quite possible therefore, that the moderate lesions observed in the earlier months after treatment, may progress to more serious ones later on. It would seem a wise procedure, therefore, when such moderate lesions are discovered, for the patient to be subjected to a series of ureteral dilatations as prophylaxis against further ureteral contraction and serious damage to the kidneys. Experience with this work, however, has shown that unless patients are suffering considerable pain, which frequently is not the case, they are very reluctant to submit to such prophylactic treatment.

One other point of value is shown in Table VIII, namely that as in the case of the bladder lesions, there is no very striking correlation between the amount of irradiation and the severity of the lesions.

TABLE VII. A COMPARISON OF STUDIES OF THE UPPER URINARY TRACTS BEFORE AND AFTER TREATMENT IN THE SAME SIXTEEN PATIENTS

STAGE OF CARCINOMA	NUMBER OF CASES		IMPASSABLE URETERAL STRICTURE	URETERAL DILATATION	PELVIC DILATATION	FUNCTION-LESS KIDNEY
I	8	Before	0	0	0	0
		After		1 12.5%	2 25.0%	0
II	5	Before	0	0	0	0
		After	1 20.0%	2 40.0%	2 40.0%	0
III	4	Before	0	0	0	0
		After	0	1 25.0%	0	0
Total	17	Before	0	0	0	0
		After	1 5.9%	4 23.5%	4 23.5%	0

#### CONCLUSIONS

From the above studies the following conclusions seem justified:

1. That the presence of lesions of the upper urinary tracts before treatment in patients with carcinoma of the cervix is of grave prognostic significance.

most authors between cured and uncured patients, and second because as yet no reports, so far as I have been able to determine, have been published in which there was a control series studied before treatment. The latter criticism is applicable to the previous report made by the author,<sup>6</sup> and the former to an otherwise very excellent report by Graves, Kickham, and Nathanson.<sup>15</sup> These authors reported 70 per cent of ureteral obstruction in a series of 257 patients studied, but it seems quite clear from their report that in most of their cases the obstruction was due to carcinoma. Bugbee<sup>16, 17</sup> has reported two groups of 8 patients each, in whom he had observed ureteral occlusion and upper tract damage following irradiation of the cervix, but none of the patients in the second group, and only 3 of those in the first seemed to be free of carcinoma. Colby<sup>13</sup> found 35.1 per cent of ureteral obstruction, Herger and Schreiner<sup>4</sup> 50 per cent, and Faerber<sup>2</sup> 56 per cent and 72 per cent of hydronephrosis, but these studies were upon advanced cases, and the urinary tract damage could be directly attributed to the carcinoma. Furthermore in 1926, Martin and Rogers,<sup>18</sup> in an attempt to prove the danger of implanting permanent needles or points directly into the parametria, experimentally demonstrated the dosage of irradiation necessary to produce partial and complete occlusion of the ureter in dogs, when the radium capsule was implanted directly in contact with the ureter. It was found that up to 2.5 skin erythema doses could be so applied without damage, and they claimed that with the ordinary methods of application little more than 1.5 erythema doses of irradiation reached the ureters.

Despite contentions to the contrary, however, such autopsy findings as that reported by Hunner and the author<sup>5</sup> and a strikingly similar case reported by Schmitz,<sup>19</sup> together with cases where the irradiation was administered for benign lesions such as have been reported by Bugbee,<sup>16</sup> Kretschmer,<sup>20</sup> and myself,<sup>6</sup> seem strongly to indicate that irradiation therapy does at times lead to ureteral occlusion and severe damage of the upper urinary tracts.

The results of the study of the present material as regards this phase of the subject are shown in Tables VI, VII, and VIII. The observations on patients originally suffering from Stage III carcinoma, as shown in Table VI, would lead

TABLE VI. SHOWING A COMPARISON OF STUDIES OF THE UPPER URINARY TRACTS BEFORE AND AFTER TREATMENT

STAGE OF CARCINOMA	TIME OF STUDY	NO. OF CASES	IM-PASSABLE URETERAL STRICTURE	URETERAL DILATATION	PELVIC DILATATION	FUNCT-IONLESS KIDNEY	TOTAL CASES WITH ANY TYPE OF UPPER TRACT LESION
I	Before	9	0	0	0	0	0
	After	14	1 7.1%	3 21.4%	4 28.6%	1 7.1%	5 35.7%
II	Before	9	0	0	0	0	0
	After	8	2 25.0%	4 50.0%	4 50.0%	1 12.5%	5 62.5%
III	Before	28	5 17.8%	12 43.0%	10 35.7%	3 10.7%	16 57.1%
	After	11	0	6 54.5%	3 27.2%	0	6 54.5%
Total	Before	46	5 11.0%	12 26.0%	10 21.7%	3 6.5%	16 34.8%
	After	33	3 9.0%	13 42.4%	11 33.3%	2 6.0%	16 48.4%



TABLE VIII—CONT'D

CASE	AGE	ORIGINAL STAGE OF CARCINOMA	STUDY BEFORE TREATMENT	IRRADIATION		TIME BETWEEN TREATMENT AND STUDY	LESIONS FOUND	CONDITION OF CARCINOMA
				RADIUM IN MC. HR.	X-RAY IN R. UNITS			
K5418	54	III	0	Gold points in parametria 4500 I and C		5 yr. 2 yr.	Ureters moderately dilated. Fig. 14	Apparently controlled
146745	43	III	0	Not known	Not known	42 mo.	Moderate bilateral dilatation of pelvis and ureters. Fig. 15	Well
155849	?	III	0	2040 I	11,895	36 mo.	Ureters moderately dilated	Questionable
155620	42	III	Neg. Fig. 16	3595 C	10,340	6 mo.	Ureters moderately dilated. Fig. 17	Apparently arrested

3. That approximately 50 per cent of patients so treated show evidence of some obstructive lesions involving the lower ureters with resulting dilatation of the kidney pelvis and the ureters above the point of obstruction, but that again in only about 15 per cent are these lesions sufficiently severe to be of clinical importance.

4. That the incidence of 15 to 20 per cent of serious urinary tract lesions in patients cured of carcinoma of the cervix is sufficiently high to render routine urologic study of such patients a justifiable and important part of the follow-up procedure.

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2. That approximately 50 per cent of apparently cured patients who have been treated for carcinoma of the cervix by irradiation show evidence that the urinary bladder has been affected by the treatment, but that only about 20 per cent show effects that are of any serious significance.

TABLE VIII. INDIVIDUAL RECORDS OF PATIENTS SHOWING UPPER URINARY TRACT LESIONS AFTER IRRADIATION

CASE	AGE	ORIGINAL STAGE OF CARCINOMA	STUDY BEFORE TREATMENT	IRRADIATION		TIME BETWEEN TREATMENT AND STUDY	LESIONS FOUND	CONDITION OF CARCINOMA
				RADIUM IN MC. HR.	X-RAY IN R. UNITS			
U73296	30	I	Neg.	2000 C*	0	9 mo.	Moderate dilatation of rt. ureter and pelvis	Apparent cure
116651	50	I	Neg.	1000 I 2000 C	500	10 mo.	Moderate right hydro-nephrosis	Apparent cure
K96211	24	I	0	2700 C	0	10 mo.	Moderate bilateral dilatation of ureters and pelvis. Fig. 12	Well 2 yr.
U43971	36	I	0	3300 I & C	0	26 mo.	Complete occlusion of rt. ureter; functionless rt. kidney. Fig. 1	Well 44 mo.
137399	41	I	0	3100 I & C	0	30 mo.	Moderate bilateral dilatation of ureters and pelvis	Well 46 mo.
149343	55	II	Neg.	3109 I & C	8,400	5 mo.	Moderate dilatation left ureter and pelvis. Fig. 2	Apparently controlled
U10901	33	II	Neg.	2965 I & C	0	6 mo.	Moderate bilateral dilatation of ureters and pelvis. Fig. 13	Apparently controlled
135255	64	II	Neg.	2400 C	10,340	46 mo.	Ureter could not be catheterized	Apparent cure
K97218	35	II	0	2800 I & C	25,920	24 mo.	V-V fistula. Left ureter occluded. Left kidney functionless. Hydro-ureter and hydro-nephrosis, rt. Fig. 4	Apparent cure
110917	57	II	0	2870 I & C	11,960	20 mo.	Bilateral hydronephrosis and hydro-ureter. Fig. 3	Apparent cure
150189	58	III	0	3699 I & C	6,000	8 mo.	Marked dilatation right pelvis and ureter. Moderate dilatation left pelvis and ureter	Local cure Bowel met.
127093	58	III	0	2600 C	0	42 mo.	Encrusted cystitis. Slow excretion. Very large hydro-ureter and hydro-nephrosis, bil. Fig. 5	Carcinoma well

\*I, Intracervical; C, contracervical.

mm. screening, 10 mg. needles with 0.5 mm. screening). The original biopsy is made with the least possible disturbance of the local lesion, and the area from which the specimen is taken is immediately cauterized. For these reasons we believe that the present methods have improved, and that, with better understanding of equipment, appreciation of the need of an accurate measure of filtration and increasing ability to deliver to the depths of the pelvis an adequate dose of the gamma rays, we may hope for better results.

It can be observed that we have been influenced by those pre-eminent figures in cancer therapy, Heyman abroad, Ward, Healy, Lynch, Taussig, Burnam and others in this country. Our statistics have been published from time to time, and what we lack in numbers may, to some extent, be made up by the fact that we have personally examined and kept under repeated observation each of the patients included in this report. Our total follow-up is 97.1 per cent of the patients seen and 98.2 per cent of those treated.

As stated, the phase of the results of radiation that we wish to discuss in this paper is the rôle that repeated radiation for recurrence plays in cancer statistics. A critical review of our patients treated radiologically for cancer of the cervix from this standpoint surprised us with the relative frequency with which prolongation of life has resulted from such a procedure. In our previously published end results, patients who had survived for five years or longer with or without reradiation for recurrence, and alive at the time of the reports, were included as usual in the percentage of absolute and relative cures. In view of the frequency with which patients have been reradiated during the period of salvage, whether it be for five or for ten years, the question has come up with us as to whether it would give a clearer understanding of the situation if it became customary to report: (1) The percentage of all patients living for five years or longer after a single course of therapy, and without evidence of recurrence; and (2) the percentage of all patients living for five years or longer, including those who were treated for recurrence during the observation period. Upon this basis the following data are submitted.

### RÉSUMÉ

Two hundred and forty-eight patients with carcinoma of the cervix were admitted for treatment to the Gynecologic Ward at Jefferson Medical College Hospital from 1921 to 1934. Fourteen of these patients were untreated for various reasons, and 7 were treated primarily with surgery. For our immediate purposes, and in order not to confuse the issue with operative treatment, these 21 patients have been excluded from this study which primarily deals with radiated and reradiated patients. (Table I.)

TABLE I. CARCINOMA OF CERVIX, GYNECOLOGICAL WARD SERVICE

Patients admitted	1921-34	248
Untreated	14	
Treated with surgery	7	21
Treated with radiation		<hr/> 227
<i>Follow-up</i>		
Patients seen	97.1 per cent	
Patients treated	98.2 per cent	

## THE INFLUENCE OF REPEATED RADIATION ON THE SALVAGE STATISTICS OF CARCINOMA OF THE CERVIX\*

LEWIS C. SCHEFFEY, M.D., PHILADELPHIA, PA.

**I**N THE study of carcinoma of the cervix, there has been a constant endeavor to reach a clearer and more complete estimate of the results of treatment. The term "cure" has been given up since one can never be sure when that point has been reached. We speak of "salvage" as representing the number of years at the end of which the patient is alive and apparently free of the disease. The trend toward a more complete understanding of the effect of cancer therapy was shown a year ago by Kimbrough who pointed out the fact that 20 per cent of the five-year survivals among a series of patients observed at the Hospital of the University of Pennsylvania subsequently died of cancer. Similar findings at Jefferson Medical College Hospital were presented by the author in discussion.

In 1936 Lynch suggested another viewpoint that has impressed us at Jefferson. This dealt with reradiation. He said "Cases are reported as five-year cures, although they have received several courses of roentgen therapy, or have been reradiated during what is intended only for an observation period to determine the efficiency of the chosen therapy." It is of this reradiation and its influence upon salvage statistics that we wish to speak.

We have for a long while followed the plan of Ward, Farrar and Sackett in personally observing cancer patients at appointed intervals after treatment and of reradiating those in whom recurrences were detected. Our statistics deal with comparatively few cases when compared with those of Heyman, Healy and Ward, numbering but 248 from 1921 to 1934. This figure includes all patients with cervical cancer seen in the gynecologic ward service at Jefferson Hospital, and, with few exceptions, treated by Dr. Anspach and myself. During this time our ideas relative to treatment have undergone considerable change for various reasons and in certain details. In the beginning, operative treatment still seemed desirable in some instances and a few patients were subjected to panhysterectomy, but since 1924 we have depended entirely upon radiation. At the outset, and during the period covered by this report, our available radium was in capsules screened with silver and brass (0.3 mm. of silver, 1.0 mm. of brass), and with Monel metal needles (0.3 mm.). We knew very little about filtration. Neither was the deep x-ray therapy the efficient means of radiation that it is at present. For the past few years we have been using high voltage x-ray therapy prior to the application of radium, now screened with platinum (50 mgm. capsules with 1.5

\*Read at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

3. The relative five-year salvage rate of patients in the Jefferson clinic, receiving a single course of radiation therapy and remaining free of recurrence thereafter, is 9.2 per cent.

4. The relative five-year salvage rate, including the group of patients whose prolongation of life has been dependent upon reradiation for recurrence, is 17.1 per cent.

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#### DISCUSSION ON PAPERS BY DRS. EVERETT AND SCHEFFEY

DR. GEORGE GRAY WARD, New York, N. Y.—What proportion of urinary tract damage is due to irradiation therapy alone and what to the extension of the disease is not easy to determine without the aid of an exploratory laparotomy or autopsy finding. We have abundant proof that ureteral obstruction and resulting kidney damage results from extension of the disease in a large percentage of cases. Notable is Ewing's statement that "the natural termination of most cases of uterine cancer is through uremia from occlusion of the ureters." This has been confirmed by autopsy studies made by many, notably by Wagner, as far back as 1868, by S. Warren, and recently by Behney in his study of 166 cases and by Graves at the Pondville Clinic.

Graves and his co-workers in the Pondville Hospital believe the cause of the ureteral obstruction in most cases is the encroachment of the tumor, but it is also probable that edema following irradiation may precipitate complete obstruction where previous partial obstruction existed due to the disease. Late occlusion may be due to fibrosis from radium or replacement fibrosis following regression of the tumor.

The responsibility of interstitial radiation with needles for ureteral obstruction must be considered. Martin and Rogers' work in 1936 showed that a 1.5 erythema skin dose reaches the ureter with ordinary needle methods and that 2.5 erythema skin dosage can be applied without damage. At the Woman's Hospital it has been our practice to use interstitial radiation with platinum needles in the majority of cases, yet a study of our results does not show a higher percentage of ureteral involvement than most clinics.

Sackett, of our clinic, reported in 1935 complications following radiation therapy in 688 of our cases, and found that the bladder and urethra were involved in 9.8 per cent, and the upper urinary tract in 5.6 per cent. These figures included many transitory symptoms. In 127 cases destined to be five-year cures there were 8.7 per cent bladder and urethra complications, and in 42 ten-year cases there were 4.8 per cent. Patients with upper urinary tract involvement showed in 5.5 per cent five-year survivals, and 4.8 per cent ten-year cures.

I have recently made an analysis of the kidney and ureteral complications in 798 cases of carcinoma of the cervix which we have observed in the Woman's Hospital Clinic from 1919 to 1937.

Of these 798 patients 55 had transitory or permanent kidney or ureteral involvement, or about 7 per cent. These 55 were distributed among the various classes according to Schmitz as follows: Class 1, 3; Class 2, 4; Class 3, 46; Class 4, 2.

Nine of these had or developed fistulas from the carcinoma or radium or both, which implies bladder infection. Of these, 5 were cases of cancer of the cervical stump. One patient was treated by a Wertheim operation with x-rays and two had

TABLE II. RADIATION TREATMENT

	PATIENTS	
Single radium treatment	112	
Multiple radium treatment	22	
Roentgen ray treatment	25	
Radium and roentgen ray treatment	68	227
Subsequent to single radium treatment	43	
Subsequent to multiple radium treatment	18	
Preliminary to radium treatment	3	
Preliminary and subsequent to radium	4	68

TABLE III. RESULTS

39 patients are alive, 5 to 16 years after initial treatment.

Of these, 21 (53.8 per cent) are without evidence of recurrence since the initial treatment, and represent a five-year relative salvage rate of 9.2 per cent.

Inclusion of the remaining 18 patients (46.2 per cent) whose lives have been prolonged by reradiation during the observation period reaches a five-year relative salvage rate of 17.1 per cent.

Two hundred twenty-seven patients were treated with radiation; 134 received radium only, 22 of whom received two or more applications for recurrence at varying intervals; 25 received roentgen ray therapy only; 68 received a combination of radium and x-ray. The roentgen radiation in 43 of these was given subsequent to a single radiation with radium; in 18 it was subsequent to two or more radium applications; 4 received roentgen radiation before as well as after the radium application; 3 received roentgen radiation preliminary to radium. (Table II.)

Of the radiologically treated patients, 39 are alive from 5 to 16 years. Of these, 21 (53.8 per cent) received a single treatment with radium and have survived without evidence of recurrence for the period stated. (Three additional patients died at the respective ages of 70, 67, and 64—10, 12, and 10 years after the single primary treatment, from causes presumably not cancer, but they have not been included in our salvage statistics.) Of the other 18 patients (46.2 per cent), 4 at present show recurrence of the disease 6, 8, 12, and 15 years after the primary treatment and have been reradiated recently, while 14 show no recurrence at present but have received reradiations in the past with radium, x-ray, or both at intervals of from 3 months to 7 years after the primary treatment. (Six additional patients received single radium treatments and lived for 5 to 8 years, and 5 received reradiations with radium and x-ray, and lived for 6 to 10 years, but all died eventually of cancer.) (Table III.)

We find therefore, upon revision, that only 21 patients have had a single course of treatment, and yet never exhibited any evidence of recurrence during an observation period of 5 to 16 years. This group represents at present our relative five-year salvage which stands at 9.2 per cent. If those patients whose prolongation of life has depended upon re-treatment are included, we reach a relative rate of 17.1 per cent.\*

#### SUMMARY AND CONCLUSIONS

1. An incomplete estimate of five-year salvage may result when statistical reports do not take into account the prolongation of life that results from repetition of treatment within the observation period.

2. In our experience, 53.8 per cent of 39 patients alive from 5 to 16 years after initial radiation treatment for carcinoma of the cervix received a single course of therapy. The prolongation of life in the remaining 46.2 per cent has followed reradiation for recurrence during the observation period.

\*When all of the 248 patients seen and the 234 patients treated (including those primarily operated upon) are considered, 41 are alive from 5 to 18 years. Twenty-one of these patients have had a single course of therapy and have never exhibited recurrence during the observation period. The five-year salvage of these patients is represented by an absolute rate of 8.4 per cent and a relative rate of 8.9 per cent. The inclusion of patients whose lives have been prolonged by re-treatment represents an absolute salvage rate of 16.5 per cent and a relative rate of 17.5 per cent.

## MANAGEMENT OF ACUTE PUERPERAL INVERSION OF THE UTERUS\*

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(From the Margaret Hague Maternity Hospital)

ALTHOUGH puerperal inversion of the uterus is said to be one of the rarest obstetric complications, many papers on it have appeared since the turn of the century. Several of the eminent members of this Society have written articles thoroughly competent scientifically and of great literary merit. There are only two reasons why another and less seasoned essayist should attempt further exposition of the subject.

First, it has been well said that no man has seen enough of these cases to know very much, of his own knowledge, about them. Hence, a few more cases detailed and analyzed, with suitable expression of tendencies toward conclusions derivable therefrom, may still have value.

Second, all truth, no matter how thoroughly known to the leaders of medical thought, must be reiterated again and again before it becomes so thoroughly impressed on the rank and file of practitioners as to be available for the benefit of all patients.

*Definition.*—The usual division of puerperal inversion of the uterus into acute and chronic stages by a time interval of four weeks after onset, is arbitrary and valueless. Kellogg has pointed out the necessity of recognition of a time sequence of pathologic events in the determination of management. This pathologic sequence is typically somewhat as follows:

1. Inversion occurs.
2. Usually after an appreciable, but not generally very long interval, *shock* of greater or less degree supervenes.

It is during the above described interval that:

- a. Recognition of the inversion is of paramount importance;
- b. Shock treatment may be anticipated or commenced;
- c. Restitution may often be quickly and easily carried out.

After some further time interval, if there is survival of initial shock,

3. Incarceration by edema and contraction of the cervical ring develops. This may be followed in turn by
4. Strangulation,
5. Necrosis, superficial or massive,
6. Local and systemic infection.

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\*Read, by invitation, at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1930.

no treatment. Three had an associated tuberculosis, one of the kidney, one of the lungs, and one in a cervix with adenocarcinoma.

A careful review of the histories and follow-up notes shows 11 undoubtedly had an involvement of the urinary tract before irradiation. Four were probably due to radium therapy alone, and 41 were probably an extension of the disease.

Ten were perhaps due to radium and the carcinoma combined. No needles were used in 16 cases.

I am in accord with Dr. Everett's statement that the presence of lesions of the upper urinary tracts before treatment is of grave prognostic significance, and his advocacy of a pre-treatment study of the urinary tract, and in the follow-up as indicated, is essential in all cases and is now our custom.

I take it that Scheffey believes we should count as so-called "cured" cases only those who after the initial treatment have no recurrence throughout the five-year period. If a patient requires subsequent reradiation during the five-year period and is free five years after the last reradiation, it seems to me we are warranted in including it in the five-year so-called "cured" cases. I dislike the term "cured" and for a number of years in our reports we use the word "salvaged." Perhaps "arrested" would be a better term as a number of patients die from cancer long after the so-called five-year survival.

DR. WILLIAM P. HEALY, NEW YORK, N. Y.—We have always known that the majority of patients with cancer of the cervix of Groups 3 and 4 die from renal complications. Very few of us have any actual knowledge of the frequency with which these patients are living on a single kidney, and we will not know unless we do routine pyelograms. We must do this investigation as part of our routine preliminary check-up, but it will not change our method of therapy. It will merely give us additional prognostic knowledge. We cannot change our therapeutic method because the cancer which is present is infiltrating not in any one direction but in all directions and must of necessity involve the bladder base and the radiation must extend into the field in which we think the cancer is progressing.

One of our important sources of trouble is definitely that of infection with our radiation. I have just briefly reviewed our last five-year series for 1933. There were 125 primary cases in that year and we had only five vesicovaginal fistulas. All of those patients are dead, and they all died within the five-year period. The fistulas were perhaps somewhat hastened by the use of radium, but they were caused by cancer which continued to grow. It was the disease and not the fistula, of course, that terminated the patient's life.

There were two vesical ulcers in the second and third year following treatment. Both of the ulcers healed under simple therapy. One additional ulcer with cancer of the rectum resulted in death. There were 10 patients in that series five years ago who showed urologic involvement of major importance, and 8 of the patients died within five years of treatment of the carcinoma.

DR. EVERETT (closing).—It is generally acknowledged that the majority of urinary tract lesions encountered in patients with carcinoma of the cervix are due to the carcinoma rather than to the treatment. I believe that in a small percentage of cases there is damage which may, or may not, be due to the treatment, but which is not due to progressing carcinoma as such a condition no longer exists.

I do not want any one to get the idea, as I am afraid was done from my original paper in 1933, that I am criticizing irradiation. I do believe that of the patients who die, a small percentage are lost not because of the carcinoma, but as a result of the urinary tract complications, whether these result from an inflammatory process or a cicatricial scar. I believe that if the patients who seem to be responding to treatment are subjected to routine urologic study, and if upper urinary tract lesions are followed with ureteral dilatations, we may be able to increase the percentage of our salvaged cases.

DR. SCHEFFEY (closing).—I am glad that Ward supported me in regard to the use of the word "cure"; we rather like the term "salvage." The expression "arrested case," as mentioned by Ward, might well be employed in certain instances.



This pregnancy had been normal except for some dyspnea due to heart disease. At term, first stage began at 3:40 A.M., May 3, 1933; she was admitted at 10:30 A.M.; membranes ruptured at 2:21 P.M. same day. At 3:21 P.M. she delivered a healthy, living girl baby, weighing 3,060 gm. by elective low forceps. Placenta and membranes were expelled completely at 3:32 P.M. the same day. The cord was of the "usual" length and showed no knots or loops. A median episiotomy was performed. Open ether was the anesthetic. She was delivered by an intern. "At approximately thirty minutes after the completion of the third stage the patient's pulse was 140; blood pressure was taken and we were unable to obtain it. The attending doctor was notified. Morphine grain one-quarter was given, 300 c.c. 25 per cent solution glucose was advised; typing and donors were ordered. Patient's color was poor; pulse was rapid and weak. Caffeine (grains 4) was given, and following the infusion of 300 c.c. of 25 per cent glucose, patient was greatly improved. Pulse was 110, fairly strong; blood pressure very low and indefinite. Uterus was relaxed and ballooned up intermittently, and there was a very slow ooze—not an alarming amount. A large clot was expelled. It was decided to pack patient. She was taken to the delivery room, where examination revealed an inverted uterus and bleeding. One thousand cubic centimeters of 10 per cent glucose was started but only a very small amount was given when the patient rapidly became worse and died of air hunger." \*

Excerpts from autopsy report: "... Tubes . . . are markedly congested and drawn into a crater-like cavity over the uterus. The uterus presents a striking picture as the fundus is depressed, and both broad ligaments are drawn into this depression. Only the fimbriated ends of the congested tubes can be seen. Uterus measures approximately 9 cm. in length. The crater . . . 14 by 11 cm. . . . Cervical ring has practically disappeared. Wall of the uterus is very flabby, soft. . . . Uterine fundus is uniformly thin, averages 1 cm. Around the fundus there is a firm ring of the uterine wall measuring 4 cm. in thickness. Microscopic sections show edema and well-preserved muscle cells, otherwise no pathologic changes. . . ."

It is only fair to recognize that chronic rheumatic heart disease, with some symptoms of decompensation, had been recognized clinically in this patient. Autopsy showed extreme deformity of both mitral and aortic valves, and advanced myocardial fibrosis. How much or how little all of this may have contributed to the fatality we do not know. She certainly was not an especially good risk to stand the strain of much hemorrhage and shock.

CASE 3.—M. P. (No. 12656), gravida iii, aged 32 years, white. Obstetric history, first child 6½ pounds, spontaneous delivery. Second child, 9½ pounds—"had trouble." "St. Cecelia Hospital, Humboldt and Richardson Streets, Brooklyn, N. Y., July 11, 1933. . . . Our records show that she had had a severe post-partum hemorrhage which had to be controlled by packing. The delivery was spontaneous in O.L.A."

During this pregnancy she had had headache and spots before the eyes. Pains began at term, 4 A.M., July 5, 1933. She was admitted to the hospital at 7:25 A.M. and delivered spontaneously a 2,800 gm. girl at 2:29 P.M. the same day. During labor a large cystocele, and procidentia were evident, the anterior lip of the cervix appearing in the vulva.

"About ten minutes following the delivery of the child the placenta appeared to be in the vagina. The fundus was massaged and some pressure made from above. No movement of the placenta was noted. Shortly after there was a small rush of blood from the vagina. Thinking that separation had taken place, pressure was again made from above and a 'normal amount' of tension on the cord from below. The placenta was delivered, and in addition there was apparently an acute inversion of the uterus, as the fundus could not be felt abdominally. Following this there was a hemorrhage amounting to about 1,500 c.c. into the membranes and placenta basin; forty minutes after delivery of the child the uterus was replaced manually after the placenta had been manually separated from the uterus. The vagina was packed (4 packs), 1,000 c.c. intravenous glucose given,

All of these may occur severally or in combination. The time embraced by the whole sequence may vary greatly. Bland states that he has seen massive necrosis supervene in a few hours, while, on the other hand, cases in each of these stages of pathology have presented themselves after intervals of months or years.

It is perfectly obvious that on the occurrence of the accident, we are dealing with a purely mechanical status, of itself relatively simple and innocuous in nature. It quickly, however, becomes urgent, due to hemorrhage and shock. This only is the acute stage of inversion as a pure mechanical entity, capable of treatment concerned only with this mechanism.

As soon as any further pathologic changes whatever occur, one is dealing with a complicated situation comparable to strangulated hernia, appendicitis with rupture, or typhoid perforation. One is now forced to predicate management, as in the other situations cited, on the complications and not the original entity.

At just what arbitrary later time one cares to call chronic, a persistence of any of these complicated pictures, I care not at all. But I do consider it most important to emphasize the above distinction between uncomplicated and complicated inversion.

The general knowledge and beliefs as to puerperal inversion fall into a fairly definite pattern, but on several important points in this pattern there are sharp divergencies of opinion. Instead of reviewing the whole of a subject which has been so often and competently reviewed before, it is proposed to present herewith in brief detail, nine cases of acute puerperal inversion of the uterus not heretofore published. The evidence which they constitute bearing on controversial points will then be assessed and certain conclusions stated.

CASE 1.—A. W. (No. 3178), primigravida, aged 25 years, white; present pregnancy said to have been normal; a private case.

Pains began at 2 A.M. on Feb. 8, 1932, with simultaneous rupture of the membranes. She was admitted to the hospital at 7:30 A.M. the same day. She continued in labor for more than twenty-four hours, at the end of which time there had been twelve hours of full dilatation and active uterine effort without advancement. There was midpelvic arrest in direct occiput posterior. Under ether anesthesia a "modified Scanzoni" was done, a 3,750 gm. baby being delivered at 10:21 A.M., February 9, by a consultant. Nine minutes later the operator suggested that the attending doctor attempt a Credé maneuver. "He gave . . . a shove and the whole uterus came out, with the membranes and placenta attached. I immediately stripped them from the uterus and replaced the latter." There was no shock. The patient's highest temperature was 100° F. on the day of delivery, and she was discharged to the care of her own physician on the tenth post-partum day.

This patient was readmitted at thirty-eight weeks, Aug. 28, 1938, six and a half years after the inversion, in the private care of another physician, and delivered in less than four hours spontaneously, a 3,611 gm. baby, in O.L.A., ran an amorbid post-partum course, and was discharged on the tenth post-partum day.

CASE 2.—E. F. (No. 13239), gravida ii, aged 31 years, white. At nine years of age she had rheumatism, for which she had been bedridden, one year. This was followed by rheumatic heart disease; general history was otherwise negative. She had delivered one child, spontaneous breech, ten years previously.

CASE 6.—H. W. (No. 13023), white, gravida iii, aged 28 years. First child weighed  $9\frac{1}{4}$  pounds, and was delivered after a forty-eight hour labor by forceps.

The second labor was in this clinic. The membranes ruptured at 11 A.M., June 5, 1933, she began to have pains a half hour later; was admitted at 1:05 P.M. the same day; delivery was spontaneous; a 4,620 gm. boy in O.L.A.; there was 400 c.c. post-partum hemorrhage; she was discharged on the ninth post-partum day.

On the present occasion at 12:30 A.M. June 20, 1935, thirty-six weeks pregnant, after an uneventful prenatal course, patient "began to bleed spontaneously, for no discernible cause; no pain. Membranes unruptured. Amount of blood loss, 'at least a pint.' Bleeding has continued since onset. . . ." She was admitted to the hospital at 2:25 A.M. the same day.

The bleeding continued only slightly after admission and the patient was treated expectantly throughout this day, but at 7:30 A.M., June 21, the day after admission, the bleeding having been slight but persistent, the patient was taken to the delivery room. The membranes were artificially ruptured. Blood stained amniotic fluid rushed out. At 7:58 A.M. the patient delivered a cyanotic premature boy with a moderate amount of bleeding, by spontaneous mechanism in O.L.A., under ether anesthesia. It does not appear that the cause of the ante-partum bleeding had been satisfactorily determined. "Conservative methods of expelling the placenta unsuccessful, the placenta being adherent. Credé's method attempted, with the least possible traction on the cord, but the placenta still adherent to the uterus." The resident was advised. The patient continued to bleed moderately and further attempts to expel the placenta were unsuccessful. Uterus became inverted, and the adherent placenta was removed manually, being peeled off gradually at 8:30 A.M. [by the resident]. At 8:35 A.M. the uterus was replaced [by the senior resident] and packed. The patient went into shock and shock treatment was immediately given—adrenalin, caffeine, sodio-benzoate, heat applied, 300 c.c. of glucose given, then 500 c.c. of normal saline. The patient lost a total amount of about 800 c.c. of blood; transfusion of whole blood was given; patient showing improvement after transfusion. Her temperature was at no time above  $100.2^{\circ}$  F., and this only on two occasions. She was discharged on the tenth post-partum day, July 1; seen once in post-partum clinic July 24. Her premature baby died the day after birth.

This patient has had no further pregnancies. Periods began two months after delivery and have been regular but severely painful. She also complains of a severe pain on the right side which occurs every two or three months but has no relation to her menstruation. She has had no medical care since she left the hospital and says she does not want to have any more babies.

CASE 7.—B. M. (No. 29892), white, gravida v, aged 39 years.

Four previous normal deliveries.

Labor began at 2 A.M., July 9, 1937; admitted to hospital at 6 A.M. the same day. There was a spontaneous delivery in O.R.A. at 12:45 P.M. the same day, under gas-oxygen-ether anesthesia.

"Following spontaneous delivery of baby, attempt was made to deliver placenta ten minutes after birth. At first Credé's maneuver, fetal surface of placenta appeared at vulva; following second Credé without cord traction, the uterus inverted completely." The attending physician was notified. "On inspection the uterus was completely inverted, the placenta attached to fundus, and one-half of it had separated from the anterior wall, the opening of the membranes was around the base of the inverted fundus, the space between being filled with blood. Within twenty minutes after inversion the uterus had been replaced [by an assistant obstetrician present]. He first pushed uterus into the vagina as a piston after the placenta had been removed, then invaginated the left side and finally the fundus entirely, using the other hand abdominally to control. The vagina was packed with two-inch gauze to hold the uterus in place. Patient was in moderate shock. The Trendelenburg posture, morphine sulfate, infusion 1,500 c.c. of 10 per cent glucose and 500 c.c. of citrated blood . . . blood pressure after operation was 114/70, pulse 120 and fair quality." Estimated blood loss 1,300 c.c. Highest temperature was

transfusion started (750 c.c.) and other usual treatment of shock was given." There was prompt good reaction. All packing was removed within twenty-four hours. She ran a low grade morbidity for three days only; was discharged on the eleventh post-partum day and followed in the post-partum gynecologic clinic until Jan. 13, 1934, five months after delivery.

About 16 months ago the patient was operated on in St. Mary's Hospital, Hoboken, N. J. The operation was the repair of the cervix, perineum and cystocele; suspension of uterus. She states that "she tries not to become pregnant," and has not in fact been pregnant since her inversion.

CASE 4.—M. K. (No. 15562), primigravida, aged 21 years, white; normal pregnancy course; at term. Pains began 6 P.M., Feb. 23, 1934; admitted to the hospital at 2:55 A.M., February 23; after 11¾ hours' labor she was delivered by elective forceps in O.L.A. with median episiotomy and second degree extension. The chief resident "was called to the delivery room because the patient was bleeding more than normal (before delivery) due to a subcutaneous tear of the perineum. Under ether a median episiotomy was done, and a low forceps delivery. Eight minutes after the delivery there was passage of a medium-sized blood clot with some bright hemorrhage, advancement of the cord, and the fundus contracted. One of the interns attempted expression of the placenta, believing that separation had occurred. The fundus relaxed and then completely inverted . . . immediately given 1 c.c. adrenalin and more ether . . . the placenta was completely adherent and attached high on the anterior wall of the corpus. It was rapidly separated and the fundus pushed back. The contraction ring had not yet formed so that the manipulation was without difficulty. There was not 50 c.c. of blood lost during the time of separation of the placenta and the correction of the inversion. . . . I believe the cause of the inversion was slight pressure on a relaxed fundus. There was no traction on the cord nor was the fundal pressure very great. The total blood loss was about 300 c.c. . . . Patient never went into shock. . . ." There was a mild morbidity for the first four post-partum days and patient was discharged in good condition on the seventeenth post-partum day.

She had a normal spontaneous delivery in O.L.A. of a 4,030 gm. baby after a fourteen hour labor, June 12, 1936, two years and four months after the inversion.

She had a normal spontaneous delivery in O.L.A. of a 3,600 gm. baby after about a two-hour labor Nov. 8, 1937, three years and nine months after the inversion.

CASE 5.—J. C. (No. 19583), gravida ii, aged 34 years, white. Her first baby weighed 7 pounds and was born with instruments at term. On this occasion her pains began 3 A.M., Aug. 21, 1934; admitted 6:45 A.M. the same day; a baby weighing 2,220 gm. was born at 9:17 A.M. the same day, by breech extraction in sacro-L.P. "Inverted uterus—shock—hemorrhage." Amount of blood loss 500 to 600 c.c. "Patient had a relatively short labor—sacro-L.P. position, breech extraction, under ether anesthesia; following this there was an inversion of the uterus with the placenta and membranes attached. Placenta and membranes were removed; adrenalin given, uterus replaced and packed with 2 to 4 inch gauze packs. Intravenous of 1,000 c.c. of 10 per cent glucose was given. The child was a living girl. The patient's general condition was fair following delivery." Another observer notes "condition on leaving delivery room poor." At any rate, at 2:45 P.M. the same day "the blood pressure was 100/44; the pulse 96, strong; the patient comfortable, fair color. At 5:15 P.M. the blood pressure was 110/75; condition good." Temperature was 100.4° F. on the day of delivery; 101.4° F. on the following day. There was no further morbidity. She was discharged on the tenth post-partum day to the care of a private physician. This patient was contacted within the past month and states there have been no further pregnancies as "she was advised against same." Her menstrual periods began three months after delivery and have been entirely regular and normal. She has severe backache at times and feels the womb is slipping down but she avoids medical care because she is fearful that the doctor might recommend an operation.

The unbelievably small figures of Zangemeister and the Dublin Rotunda have been again and again cited. Kellogg has gracefully made fun of them. Irving reports from Boston Lying-in Hospital an incidence of 1:7837 and quotes comparable figures by Maxwell at the University of California Hospital of 1:6500. Davis reports from the Methodist Episcopal Hospital in Brooklyn 1:6500 and Stander from the New York Lying-in Hospital, 1:4000.

During the period covered by the 9 cases presented herewith we have had 39,000 living births. This makes our incidence in this period 1:4,333.

Curiously, our experience has not been consistent. For the period 1913 to 1931, eighteen years, with a service in which more than 20,000 living births occurred, I do not recall or find a record of a single recognized case of acute puerperal inversion. In the last seven years, with a material less than twice as large, we have had 9 cases. I cannot reconcile this difference nor impute it to any particular difference in the handling of the material in the two periods; nor to difference in type of personnel engaged in the work.

The importance of primigravidity in the causation of acute puerperal inversion has been stressed, on the supposed basis that fundal attachment of the placenta is more common in women pregnant for the first time. Data as to the actual implantation of the placenta are incomplete or lacking in most of our cases. However, only 2 of the 9 actually occurred in primigravidas. The other cases ranged in gravidity up to five. In those cases in which the insertion of the placenta was specifically described, the attachment was only partially to the fundal portion of the corpus uteri. The higher incidence in primigravidas is not borne out in this small series.

Another disputed point is the role of mismanagement of the third stage of labor in the production of inversion. The majority of writers unequivocally state that inversion does usually depend on such mismanagement.

Irving on the other hand concludes just as definitely from his careful analysis of much collected material that this factor is of importance in somewhat less than half the cases.

I am quite ready to concede that spontaneous inversion may occur, as it apparently did do in one of our own cases. I agree very definitely with Findley and others, that the uterus must be conditioned, so to speak, by distention and relaxation before it is mechanically possible for this accident to occur. But it would appear from our experience that injudicious management of the third stage is outstandingly important. Six of our 9 cases definitely fall in this category, with 2 other cases open to question, so that possibly 8 out of the 9 were more or less directly caused by such mismanagement.

Advice as to the removal of the attached placenta before attempting replacement of the inverted uterus varies. Of our 9 cases, in 5 the placenta was completely, and in 2 others partly, adherent to the uterus. In each case the placenta was promptly detached as soon as the condition was recognized, and before attempts at reduction.

100° F. on the following day. She was discharged in good condition on the tenth post-partum day. The uterus was small, firm, well involuted, retroverted at a post-partum visit Aug. 25, 1937, but patient "had weakness, dizziness, nausea . . . does not appear . . . in the best of health . . . has puffs under the eyes, anemic."

This patient has not had any subsequent pregnancies. Her periods returned four months after delivery and vary from 18 to 28 days; flow lasting from one to two days. She does not want any more babies. She is pale, thin, nervous, appears to be anemic. She had a thyroidectomy done one year ago.

CASE 8.—A. M. (No. 19299), gravida iii, aged 22 years, white. One previous instrumental delivery after twenty-four hours of labor, of a 7¾ pound baby. One previous spontaneous delivery after a five-hour labor of a 4,480 gm. baby in O.L.A. in our own clinic, Jan. 26, 1935. Present labor began 9:15 P.M., Apr. 14, 1938, at about thirty-eight weeks. She was admitted at 3:15 A.M., Apr. 15, 1938; delivered spontaneously after fourteen hours of labor a 4,060 gm. baby in O.L.A. under gas-oxygen-ether anesthesia, with a second degree laceration of the perineum.

"Placenta showed signs of being free—bleeding—attempt made to express it. This was deferred after no results. Then the laceration was repaired. When repair was finished there was a gush of blood; several attempts made with Credé and cord traction to deliver the placenta. Efforts ceased for ten minutes. With further bleeding, more vigorous attempts at expression made, placenta being in sight. While making manual traction it was discovered that uterine wall was inverted and placenta adherent for one-third of the placental surface. Placenta was peeled off and uterus was replaced manually. Uterine packing and vaginal packing . . . total blood loss 600 c.c. Condition of patient good at this time."

There was no post-partum febrile morbidity and patient was discharged to the care of her own physician on the tenth post-partum day, in good condition. This was barely one year ago, and we have no record of further pregnancy on the part of this patient.

CASE 9.—F. L. (No. 28474), gravida ii, aged 25 years, white. She had had one child Nov. 28, 1936, at term, by spontaneous delivery on the private service in our own clinic.

This pregnancy was uneventful. She delivered spontaneously in O.R.T. after an eleven-hour labor a 2,820 gm. baby at 7:24 P.M., Dec. 22, 1938, under gas-oxygen-ether anesthesia. A right mediolateral episiotomy was repaired, after which "placenta seemed free; delivered by Schultz mechanism with moderate tension on cord and fundal pressure, after the placenta was thought to be in the vagina. Immediately after delivery of placenta the uterus was found low in the pelvis. The fingers were inserted into the vagina to push it up. A globular mass was found and an indentation recognized in the top of the fundus through the abdominal wall . . . with pressure of fingers in the center of the mass in the vagina a dimple formed and the mass gradually was reduced, with obliteration of the fundal cupping. The edges of what was thought to be the portio vaginalis cervicis were seized with forceps, and there appeared to be a laceration in this structure which was bleeding briskly . . . no solution of continuity in the uterine wall above it could be felt. This apparent rent was sutured completely; the suture appeared to adequately control all bleeding. Now, a very much relaxed atonic cervix was demonstrated below the line of suture. It was reefed together by suture on either side. It is believed that the first line of sutures was so placed as to close off the uterus at the internal os. Patient lost 600 to 800 c.c. of blood but did not show a marked degree of shock at any time." However, saline, glucose and 500 c.c. of blood were given intravenously. Patient had a temperature of 101° F. on the third post-partum day; was otherwise afebrile and was discharged on the tenth post-partum day. Uterine drainage appeared unobstructed, involution was satisfactory and rapid, and at six weeks post partum was complete and all injuries healed.

The incidence of acute puerperal inversion of the uterus is one factor concerning which there is perhaps the widest discrepancy.

there been trouble taken to detail the manner in which it was done. Most of the accounts merely state that the inverted uterus was replaced manually, one qualified by saying "without difficulty," one says that the pressure by which the taxis was accomplished was made centrally over the inverted mass; another that the initial pressure was made laterally; in all the rest we are left completely in the dark as to any special mechanism by which the apparently very casual manipulation was accomplished. It is hardly worth while then to enter into any controversy as to the best method of accomplishing taxis. The choice of optimal time for attempting it seems to be very much more important than the particular manner in which it is attempted. I am inclined to agree with Bland, who says that if one method does not promptly succeed, the other may be tried, thus placing this particular problem in the same category of trial and error in which so many obstetric problems appear to properly belong.

Four only out of the 9 patients were transfused. Probably not more than 2 were in such severe shock as to urgently need transfusion.

The cavity of the uterus was packed in only 4 patients, but in 2 others the vagina was packed.

Shock was described as severe in only 3 cases. Its degree was equivocal in 1, definitely present in 2 more, but did not appear in any appreciable degree in 3.

Blood loss would, of course, parallel the shock more or less. There were 4 patients who showed markedly excessive blood loss; 2 others in whom the blood loss was excessive and 3 who definitely did not sustain any unusual degree of bleeding.

Of the 8 survivors, 2 had no febrile morbidity whatever. In 4 others it was minimal and in the other 2 slight. All survivors left the hospital on the regular tenth day of the puerperium, except two who remained eleven and seventeen days, respectively.

The age range was nearly two decades, the youngest 21, the oldest 39. All the patients were white women. General medical history was entirely irrelevant except in one case with history of rheumatic heart disease. All the patients were at term excepting one who was at 36 weeks and another at 38 weeks. The anesthetic was ether in every case, supplementing gas-oxygen in 3 cases.

Who had the skill to replace these uteri so easily by taxis, a procedure averred to be so difficult and dangerous? One was an attending obstetrician; one was an assistant attending obstetrician—this man reduced 3 of the cases, but had been responsible for only one; 2 others were assistant attending obstetricians; the other 3 were residents.

Special procedures: Except the combatting of shock, reduction of the uterus, packing of the uterus or of the vagina, no special procedures were used in this series with two exceptions. Adrenalin was used for its supposed value in relaxing the constricted cervix in 3 cases. There would not appear to be enough difference in the difficulty experienced in the reduction in all of the cases of this series, to indicate that the use of adrenalin did actually contribute to the ease of this manipulation.

It appears from this, that danger of increased hemorrhage and shock incident to the removal of the placenta, if recognition is prompt, has been exaggerated. Full advantage should be taken of the increased facility of reduction which the removal of the bulk of the placenta affords.

The place of taxis in the treatment of acute inversion has been accepted very largely as a matter of course by many authors, among them Beck, Bethune, Bland, DeLee, Edgar, Findley, Kellogg, Phaneuf, Schumann and Williams, and several note the simplicity and ease of this maneuver.

D'Errico expresses the matter very graphically, saying that the inexperienced accoucher may waste valuable time "and the golden opportunity to attempt manual replacement at once is lost." Effort should be made to emphasize its early recognition and the technique of manual replacement, which will usually be successful if the condition is recognized early.

Barrows says, however, that "immediate replacement of puerperal uterine inversion is frequently attended with considerable shock and loss of blood and is a dangerous procedure."

Irving makes a strong argument against immediate reduction, citing much higher mortality records by this course than by others. He proposes laparotomy and reduction by Huntington's method as preferable. He at least implies that immediate manual reduction is not proper. Indeed he goes so far as to say that it is not justifiable except "in a remote farm house in a community where hospital facilities are not available."

Huntington, Irving and Kellogg say: "Manual reposition in some cases is impossible and may be accompanied by such free bleeding that it is questionable if it should be attempted."

There was one death in our series. It has already been detailed. Reinversion was not accomplished or attempted. The patient died in shock due to the tardy recognition of the condition before measures directed to overcoming the shock could be effectively put into operation.

All the other cases were reduced by taxis. There was no special difficulty in the accomplishment of this procedure in any single case. All the patients recovered and all had minimal morbidities.

We have been able to trace all of the 8 surviving patients. Of these the inversion has occurred so recently in two as not to have made subsequent pregnancy possible. One patient has had two spontaneous deliveries since the inversion. Another patient has had one entirely natural and spontaneous delivery. There have been no subsequent pregnancies among the rest.

Two patients only had anything significant in their prior obstetric history. One of them had had 3 prior deliveries, the first with forceps, the other 2 spontaneous, but the third accompanied by sufficiently severe post-partum hemorrhage as to have required transfusion. Another case had had two spontaneous deliveries prior to the one in question, the second accompanied by severe post-partum hemorrhage requiring packing of the uterus.

It is to be regretted that taxis for replacement of the inverted uterus apparently presented so little difficulty that in only two cases has



itioner, working perhaps in forlorn and isolated surroundings, to attempt to handle so serious a complication by taxis without help. Yet I am sure that, were his conditions for delivery even decent, and if he did recognize the condition as soon as it occurred, and did then promptly employ taxis and succeed in reducing the uterus before his patient became markedly shocked (which our experience has proved may readily be the case in the majority of such accidents), then his patient will be better off than if he meets the issue only half way by packing the vagina, transporting her to a more or less remote hospital, and there subjecting her to some operative procedure.

This latter course will probably be that of election in cases in which tentative effort at taxis has not succeeded, or where lack of alertness has permitted deep shock to supervene and become the paramount and determining feature of the clinical picture.

Then, shock having been overcome, Huntington's method may be used.

But in regard to really acute inversion as first defined in this paper, let us teach ourselves and our students to bear always in mind that it can happen; that we must recognize it promptly when it does, that if we do recognize it sufficiently promptly, shock will not be so severe as to prohibit definitive management; that we should immediately institute shock-combating procedures and simultaneously proceed with taxis before complicating conditions have had opportunity to set in.

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254 UNION STREET

#### DISCUSSION

DR. ALFRED C. BECK, BROOKLYN, N. Y.—Although spontaneous inversion does occasionally occur, I believe with Cosgrove that most inversions are due to mismanagement of the third stage of labor. In his series he showed that traction on the cord or pressure on the uterus was responsible for the inversion in possibly 8 of his 9 cases. In 3 of them both of these etiologic factors were operative.

In one other case, without having noted Bay Jacobs' suggestion to partly suture the external os after the reduction of acute inversion, the procedure was actually applied successively to the internal os and the external os. No interference with drainage occurred. The uterus involuted rapidly and well. The patient had a minimal morbidity and was discharged on the tenth post-partum day. Six weeks later inspection of the cervix showed perfectly patent cervical canal, with entire symmetry of the os and of the cervix itself.

It is recognized that many hundred cases of inversion of the uterus are more or less perfectly detailed in the literature, and that the present series of 9 cases is inconsiderable in comparison to this large number. It is not inconsiderable, however, as representing experience in a single clinic in a relatively short space of time. The uniformity of characteristics of these cases perhaps has enough significance to permit certain inclinations toward conclusions to be expressed.

### CONCLUSIONS

First, the greater number of inversions appear to depend on inexperienced management of the third stage of labor. They will therefore occur most frequently in the experience of less experienced obstetricians. In our own series two-thirds of them occurred in the hands of interns.

Second, prompt recognition of the identity of the lesion gives the utmost opportunity for safe management.

Because of these two broad considerations, a most important phase of the management of acute inversion is prophylaxis depending on better management of the third stage of labor.

To this end, better undergraduate emphasis, and better practical supervision in our clinics, must be focused on the best means of handling this phase of labor.

Space will not here permit any considerable discussion of the matter, but, no matter how exhaustive such discussion might be, it could be well summed up in two words, gentleness and patience.

Beyond the vital importance of such prophylactic teaching, educational emphasis should demonstrate: that the condition is not nearly so rare as has been taught; that its potential occurrence should be constantly borne in mind in the presence of suggestive symptoms (unusually prompt, persistent, or profuse bleeding appearing during, or following, the third stage of labor, irregularities in contour or position of the corpus uteri); that early recognition and prompt institution of treatment give best prognosis. Of the 8 cases in our present series in which the condition was promptly recognized and the uterus immediately reposed, all recovered. The circumstances of the death of the other case must be imputed to delay in recognition of the pathology, and institution of treatment.

Given recognition of the condition before the development of severe shock, treatment by taxis would appear to lie well within the capacity of even mediocre obstetricians. I hesitate to advise the average prac-

grove deserves high commendation for his integrity in holding that 8 of 9 cases entirely controlled by his institution were the result of mismanagement, but I believe his enthusiasm for the truth has led him astray. His clinic has had the rare experience of having 9 women with the uterine conditions which made the inversion possible, but errors of management were not responsible.

I believe it is wise to return the uterus at once to its normal position. Then, when contractions permit it, the placenta should be removed. The preliminary removal of the placenta may result in such contraction and retraction that the uterus may not be reposed. Furthermore, the retention of the placenta protects the placental site from infection during the manipulations. Some have advised that the fundus should first be dimpled so that the fundus itself is first returned, and then more lateral areas be pushed up. This means that four layers of uterine muscularis must be passed through the cervical canal. If the ring be tight, this may be an insurmountable difficulty. Most authorities advise that that portion which descended last shall first be reposed, by which process only two uterine layers pass through the cervix at a given moment.

DR. JOSEPH B. DELEE, CHICAGO, ILL.—I would recite briefly nine cases in my own experience:

CASE 1.—After manual removal of the placenta, the uterus turned itself inside out as I was drawing my hand out after revising its interior. I simply pushed it back and packed.

CASE 2.—This woman had a complete inversion which was visible at the vulva. I pushed it back and packed, and when she arrived at the hospital, the uterus had reinverted itself. She recovered.

CASE 3.—This case of inversion had five transfusions and later Spinelli's operation. Five years later I did a cesarean section before term, resected the scar which was paper-thin, and she went home with a live baby.

CASE 4.—In another case, which occurred in the hospital, the inverted uterus followed the placenta. The intern pushed the uterus back, gave ergot and pituitary, and the woman recovered.

CASE 5.—A similar case occurred in my service a few years ago.

CASE 6.—Another patient was dead from complete shock when I arrived at her home.

CASE 7.—The next patient was dead from shock and hemorrhage when my associate arrived.

CASE 8.—Another patient came into my service about the fifth day of the puerperium. As I started to remove a pedunculated fibroid which had appeared at the vulva, the uterus came down through the cervix. I pushed the top of the uterus back and packed. She recovered.

CASE 9.—The last patient came in six weeks after the birth of her baby, with sepsis and inversion. I tried to persuade her to stay in the hospital until I cured the sepsis before operating, but she went to another hospital, where she was operated upon and in a few days died of sepsis.

DR. JOSEPH L. BAER, CHICAGO, ILL.—Cosgrove very properly placed major emphasis on mismanagement as the all-important factor in etiology. Since mismanagement is charged with the responsibility of acute inversion of the uterus, the best treatment here, as elsewhere, is prevention. May I indicate a procedure which in my opinion is vital in correct institutional management of the third stage of labor.

Every well-run institution requires the recording of the minute of birth of the infant and the recording of the instillation of silver nitrate into the infant's eyes. Some require a recording of the time of the delivery of the placenta, but very few pay attention to the time of separation of the placenta.

In our clinic where traction on the cord is never allowed and where pressure on the fundus is used only when the uterus is in a state of contraction, there have been no inversions in over 30,000 deliveries. On the other hand, some of my associates who work in hospitals where the supervision is not too good tell me that they are called upon to treat this complication not infrequently. They also state that almost invariably the cause of the inversion is either traction on the cord or pressure on the uterus when the uterus is relaxed.

Cosgrove's recommendation concerning early recognition and prompt reposition is, I believe, very sound. The sooner the uterus is replaced the less should be the shock and the less should be the hemorrhage. If the manipulations are done early, the condition of the uterus should be most favorable for reposition, certainly much more favorable than later on. As a consequence the shock incident to the operation and the hemorrhage should be less. I believe that in the cases in which reposition is not attempted soon after the accident occurs, or in which the shock is very pronounced, it might be better to treat the shock and then employ the simpler abdominal technique recommended by the Boston group.

I have seen three cases which behaved very much like those presented by Cosgrove and were reported to our Analysis Committee in the past two years in Brooklyn. All of these patients, of course, died. They occurred in 77,591 deliveries in Brooklyn, giving us one death from inversion to 25,863 births. The first case was a primigravida who was delivered spontaneously. The placenta was delivered by "gentle traction" on the cord. Five minutes later she went into shock and died within a short time after the inversion had been corrected manually. The second case was also a primipara who was delivered by low forceps. The placenta was expressed by Credé's procedure, which was followed by inversion of the uterus. The vagina was then packed, but she bled through the pack. As a result, the uterus was repositioned one-half hour later, but the patient died of shock within one hour. The third patient had a precipitate labor at home at seven months, followed by post-partum hemorrhage. The ambulance surgeon expressed the placenta by Credé's procedure and caused inversion of the uterus. Profound shock followed and the patient died fifteen minutes after admission to the hospital. In all three of these cases, inversion was probably due to mismanagement of the third stage.

DR. RUDOLPH W. HOLMES, CHICAGO, ILL.—I believe it is not debatable that gross mismanagement may be a contributory factor in the production of an inversion, but I am equally convinced that such violent measures may have no effect unless there be some peculiar alterations of the muscular texture of the uterus. Such abnormalities of structure are not necessarily congenital, for repeated inversions are really unique in women during successive pregnancies.

Intestinal intussusception offers a definite parallel to the mechanics of uterine inversion. Both must have some temporary abnormalities of tone of the muscularis to permit their occurrence. Some invagination must supervene before further progress of the depressed area can occur. In the uterus, there are three areas which are peculiarly prone to be the site of an inversion: the placental site, especially if it be near the fundus, and the areas about the two ora fallopii. A depression in the uterine wall occurs and then the "rim of the cup" contracts, forcing the protruding portion more deeply into the uterine cavity. This goes on progressively until the inversion is completed, producing the so-called spontaneous active inversion. There is no question but that spontaneous inversion does occur.

The literature also contains case reports wherein the inverted uterus has spontaneously corrected itself. White, in London, had such a case over a hundred years ago. In one of my own cases, repeated taxis had failed to secure the fundal return. After resting my hands, I again assayed a reduction, but the fundus receded before my fingers, replacement occurring without pressure on my part.

Inversion is, and always has been, an extremely rare obstetric complication. If violent attempts at Credé or the worse Dublin method were material causes of inversion, every other woman in the past century, when these methods were the rule, would have had an inverted uterus. We are doing the profession a grave injustice in maintaining a responsibility upon the attendant when an inversion occurs. Cos-

## Item

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### American Board of Obstetrics and Gynecology

The written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 6, 1940, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held in June, 1940.

Candidates for reexamination in Part I (written paper and submission of case histories) must request such reexamination by writing the Secretary's Office not later than November 15, 1939. Candidates who are required to take reexaminations must do so before the expiration of three years from the date of their original examination.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J., on June 8, 9, 10, and 11, 1940, immediately prior to the annual meeting of the American Medical Association in New York City.

Application for admission to Group A, Part II examinations must be on file in the Secretary's Office not later than March 15, 1940.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

In our institution we require that the physician in charge of the delivery, whether ward service or private, announce, and the nurse record the minute of separation of the placenta. This necessitates recognition of separation of the placenta. If this is efficiently carried out, it will obviate the too violent efforts at expression of retained or adherent placenta, and this in turn will reduce the likelihood of inversion of the uterus to an unavoidable minimum.

DR. A. COSGROVE (closing).—Beek has indicated that the case histories presented here are an indictment of the type of supervision of the work of interns in our clinic. I feel, however, that if some other clinics had to accept and turn out interns under the same circumstances that we do, they also might share our unfortunate experience. I know that under Beck's very close and meticulous supervision, he will not see inversion of the uterus in his clinic.

Holmes has stressed the importance of other factors than improper handling of the third stage in the causation of inversion. Everyone who has studied the literature or his own cases will agree with what Holmes has stated. One of our own cases very definitely occurred spontaneously.

It seems to me, however, that in presenting a series of cases like this it is important to stress the remedial factors. If inversion occurs spontaneously in spite of everything that we can devise to protect the patient, then it is an unavoidable accident. But if it occurs because we have mismanaged the third stage, that is our fault, and that is the factor that should be emphasized, because it is correctable. That was my purpose in putting emphasis on that phase of the subject.

The proposal to repose the uterus before the placenta is removed, I shall have to take issue with. Dr. Holmes has earlier in his remarks stressed the importance of beginning the reduction of the uterus at the margin of the constricted ring in order to have the least possible number of layers of uterine muscle simultaneously within the grasp of the ring. It seems to me good sense to extend the logic of his technique to the avoidance of the unnecessary bulk of the placenta within the grasp of the ring. This objective can only be attained by removing the placenta before the uterus is reinverted. In our own experience, we have perhaps been lucky in the results of invariably removing the placenta before reducing the uterus. We have not encountered any instances calling the wisdom of that course into question.

*(Additional papers presented at this meeting will appear in the December issue, including those of Drs. T. K. Brown; Matthews and Acken; Collins; Allen; Schumann; Browne, Henry and Fenning. The paper by Dr. L. K. P. Farrar, on "The Condition of the Cervix in 500 Consecutive Cases of Abdominal Hysterectomy" is scheduled for publication in "Surgery, Gynecology and Obstetrics.")*

gynecologists. In the interest of conserving space we here report only 25 of these cases. It may be well first to review the curves of excretion of these substances in normal pregnancy and to discuss the interpretations which may be drawn from them as to the physiologic changes taking place.

Prolan appears in the urine almost immediately on implantation. Kurzrok and others<sup>4</sup> and Browne and Venning<sup>5</sup> showed that it could be detected ten to thirteen days after the appearance of the gonadotrophic substance which occurs just before ovulation. In another case we have found that it appeared eleven days after ovulation as approximated from the time of onset of pregnandiol excretion. The rate of excretion rises rapidly after this to reach a maximum about fifty to sixty days after the beginning of the last actually occurring menstrual period, in most cases.<sup>5-8</sup> The height of this peak varies considerably in different cases and may be as high as the concentrations formerly thought to be characteristic of chorio-epithelioma.<sup>9</sup> The maximum excretion is maintained usually for only a few days and is followed by a rapid fall. A low level is reached at about one hundred to one hundred and twenty days. Thereafter the level of excretion in most cases remains relatively constant until parturition, after which it declines to zero in five to ten days. In a few cases a secondary rise of prolان excretion occurs in the sixth to the eighth month and lasts for a varying period of time.<sup>10, 11</sup> Estrogens were found by Smith and Smith<sup>7</sup> and Mason and Gustavson<sup>12</sup> to follow the usual excretion curve of the menstrual cycle through the period of conception. The drop in excretion which was expected premenstrually was only slight, and the excretion rate rose again after the time of the missed period. Both Browne and Venning,<sup>5</sup> and Smith and Smith<sup>7</sup> found variations in some cases in the excretion of estrin in the first few months of pregnancy which they interpreted as having a cyclic character. It had been shown by Zondek that the rate of estrin excretion rises rapidly between the third and fourth months of pregnancy. It reaches a maximum in the eighth or ninth month, and disappears within a few days after labor. Browne, Henry, and Venning<sup>11</sup> found this maximum to vary between 15,000  $\gamma$  and 40,000  $\gamma$  per twenty-four hours in the cases which they studied.

Sodium pregnandiol glucuronidate is an excretion product of corpus luteum hormone and with certain limitations is believed to reflect the amount of progesterone being formed in the corpus luteum or elsewhere. This compound is absent from the urine during the follicular phase and first appears about twenty-four to thirty-six hours after ovulation. In most normal individuals the excretion lasts for ten to twelve days and the total amount excreted is between 45 and 55 mg. expressed as pregnandiol. Ordinarily the excretion stops one to three days before the onset of bleeding, but in a few cases the excretion continues up to the time of bleeding (Venning and Browne,<sup>13</sup> Wilson and others,<sup>14</sup> Hamblen and others,<sup>15</sup> Stover and Pratt<sup>16</sup>). Two cases have recently been studied by us through the period of conception. In one case in which the rate of excretion was low there was a sudden increase eleven days after the day on which ovulation was believed to have occurred; in the other case there was no appreciable change over the time of implantation. In early pregnancy the level of excretion is the same as the maximum reached during the normal menstrual cycle, that is from 5 to 10 mg. per twenty-four hours. In this connection it may be pointed out that Browne and Venning<sup>17</sup> showed that subcutaneous

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## Original Communications

### THE SIGNIFICANCE OF ENDOCRINE ASSAYS IN THREATENED AND HABITUAL ABORTION\*

J. S. L. BROWNE, M.D., PH.D., J. S. HENRY, M.D., M.R.C.O.G., AND  
ELEANOR H. VENNING, PH.D., MONTREAL, CANADA

*(From the McGill University Clinic, and the Department of Obstetrics and Gynecology, Royal Victoria Hospital)*

THE problem of the mechanism of abortion, both threatened and habitual, has been much discussed. Numerous claims for good therapeutic results from the treatment of these conditions with gonadotrophic extracts of pregnancy urine, progesterone and vitamin E, have been made. On the other hand, it has been clearly recognized by Huntingdon,<sup>1</sup> Rock,<sup>3</sup> and others that in a majority of cases of abortion the gestation is abnormal or the fetus already dead when the symptoms appear. The evaluation of the results of therapy with progesterone has been made very difficult, owing to the above-mentioned fact and also because it is not easy to determine how many cases of threatened abortion, in which the fetus is not dead at the time of onset of symptoms, will carry through with ordinary routine methods of therapy. It was thought that further light might be shed on this subject by a detailed study of some of the endocrine factors which are of importance in the physiology of normal pregnancy.

The present investigation therefore deals with a study of the excretion of prolan (gonadotrophic substance), estrogens, and sodium pregnandiol glucuronidate in the urine of 35 cases of threatened or habitual abortion. Twenty-one of the patients were under the direct care of one of us (J. S. H.). The rest were referred for assay by other

\*Read, by invitation, at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."



Studies of estrogen excretion were made by numerous investigators, and it was found by Waldstein<sup>18</sup> and von Probstner<sup>19</sup> that, while the excretion might be low immediately after operation, in the later months of pregnancy it reached normal values. A good review of the subject is given by Guldberg<sup>20</sup> who concludes that the placenta is the site of production of estrogens during pregnancy. It had previ-

200000  
RU/24 hrs.

150000

100000

50000

30000  
R.U. 24 hrs.

EXCRETION OF PROLAN  
IN PREGNANCY

20000

15000

10000

5000

DAYS 28 56 84 112 140 168 196 224 252 280

Fig. 1.—Excretion of prolan in the urine of 8 patients with normal pregnancy. The dotted part of the curve represents the two types of excretion seen in late pregnancy, with and without a secondary rise in rate of excretion.

ously been generally assumed that corpus luteum hormone was unnecessary in the later months of pregnancy, because it had been found that the corpus luteum usually degenerated about the third month. Ehrhardt<sup>21</sup> and Adler, de Fremery and Tausk<sup>22</sup> found small amounts of progesterone activity in the placenta at term and Guldberg<sup>20</sup> showed that progesterone activity was present in the full-term placenta of

injections of gonadotrophic substance from pregnancy urine (physex) given daily or every other day during the luteal phase of the menstrual cycle would prolong the corpus luteum phase, increase the output of pregnandiol, and delay menstruation. They found that the response of different corpora lutea to the same amount of injected gonadotrophic substance varied greatly. Further, that after a varying time, continuing the dose of physex at the same level failed to maintain the corpus luteum, pregnandiol excretion decreased and finally ceased and menstruation began in spite of continued injections. This led them to suggest that the corpus luteum might require increasingly large amounts of prolactin to maintain its function as it grew older, and to speculate whether the rapidly increasing amounts of prolactin formed in early pregnancy could be given teleologic significance on this basis. The time at which the excretion of pregnandiol begins to rise from this level varies considerably in presumably normal cases, but it is most often between the seventieth and ninetieth days after the beginning of the last menstrual period. The amount excreted rises usually parallel to the rise of total estrogens and reaches a maximum in the ninth month. The maximum is very variable, usually between 60 and 105 mg. per twenty-four hours, in some cases somewhat lower, and the compound disappears abruptly within twenty-four hours of delivery, but here the presence of blood may interfere with the detection of small amounts. In one case in which catheter specimens were obtained, 7 mg. were detected per twenty-four hours in the first three days after labor. Before labor in this case the value had been the usual one for late pregnancy.

Figs. 1, 2, and 3 show the values for prolactin, pregnandiol and total estrogens, with rough average curves in eight cases of normal pregnancy. Not all of these cases were assayed throughout the whole period of gestation. Table I gives the variations in the values obtained throughout pregnancy. This table is derived from the same eight cases.

TABLE I. VARIATIONS IN URINARY EXCRETION OF PREGNANDIOL, ESTROGENS AND PROLACTIN IN EIGHT CASES OF NORMAL PREGNANCY

DAYS	PREGNANDIOL MG./24 HR.	TOTAL ESTROGENS GAMMA/24 HR.	PROLACTIN R. U./24 HR.
28- 56	5- 11	200- 1,000	700- 50,000
56- 84	6- 20	250- 2,400	10,000-200,000
84-112	10- 28	800- 4,000	3,000- 28,000
112-140	13- 35	1,000- 7,000	2,000- 10,000
140-168	22- 52	3,000-14,500	1,000- 10,000
168-196	40- 72	7,500-18,000	1,000- 15,000
196-224	48- 85	7,500-23,000	3,000- 13,000
224-252	55- 95	10,000-25,000	1,000- 24,000
252-280	60-105	15,000-40,000	2,000- 10,000

Days are counted from the first day of the last actually occurring menstrual period.

It has been known for a long time that both ovaries or the ovary containing the corpus luteum could be removed and pregnancy continue to term. The time at which the ovaries have been removed varies,

a patient from whom both ovaries had been removed on the one hundred and thirty-third day. These findings suggested that the placenta might form corpus luteum hormone. In a case in which the ovary containing the corpus luteum was removed on the one hundred and fourth day, it was reported by Browne and others<sup>23</sup> that pregnandiol continued to be excreted up to term; the rate of excretion was within normal limits. Jones and Weil<sup>24</sup> confirmed this in a study of one other patient in whom the ovary was removed at the fifty-fourth day.

It was not until studies on pregnandiol were made that it was appreciated that large quantities of progesterone were being formed in late pregnancy and that it was rendered probable that most of this was being formed by the placenta.

The details of the normal values for the excretion of prolan, estrogens, and pregnandiol upon which Figs. 1, 2, and 3 and Table I are based will be published elsewhere. Consideration of the curve of excretion of prolan led Browne and Venning<sup>6</sup> to suggest a theory concerning the physiologic relations of ovary and placenta during pregnancy and with regard to the transfer of site of formation of estrogens and progesterone from ovary to placenta at about the third month. Subsequent studies on the pregnandiol excretion during the normal menstrual cycle and pregnancy, the effect of pregnancy urine gonadotrophic substance on the corpus luteum mentioned above and the effects of ovariectomy on pregnandiol excretion during pregnancy have led to a better understanding of the endocrine relations during conception and pregnancy, particularly with regard to progesterone, and to a further elaboration of the theory which is presented here.

The normal corpus luteum ordinarily begins to function between twenty-four and thirty-six hours after ovulation and continues to function for ten to twelve days. Embryologists agree that the ovum takes approximately ten days to migrate down the tube and to become implanted in the endometrium. From the time at which prolan appears in the urine during the period of conception, it is probable that the chorion begins to secrete this substance almost immediately on implantation. The prolan usually maintains the corpus luteum function at the same level as the maximum attained during the menstrual cycle, but sometimes at a slightly higher level. It will be seen from this that the time relations during conception are rather exact. If for example the corpus luteum secretes progesterone for only seven days instead of ten or twelve, then by the time the ovum is ready to implant the corpus luteum will have ceased to function and implantation will not take place, since degeneration of the endometrium or even menstruation has begun. Such a short corpus luteum phase has been observed in some patients with sterility in whom no other cause for infertility has been detected. The rapid rise in production of prolan in early pregnancy may be necessary for increased stimulation of the corpus luteum to maintain it as it grows older.

In normal pregnancy, pregnandiol excretion may begin to rise from the level obtained after implantation as early as the seventieth day or perhaps a little earlier, but in other cases the rise fails to occur

40000  
Y/24 hrs.

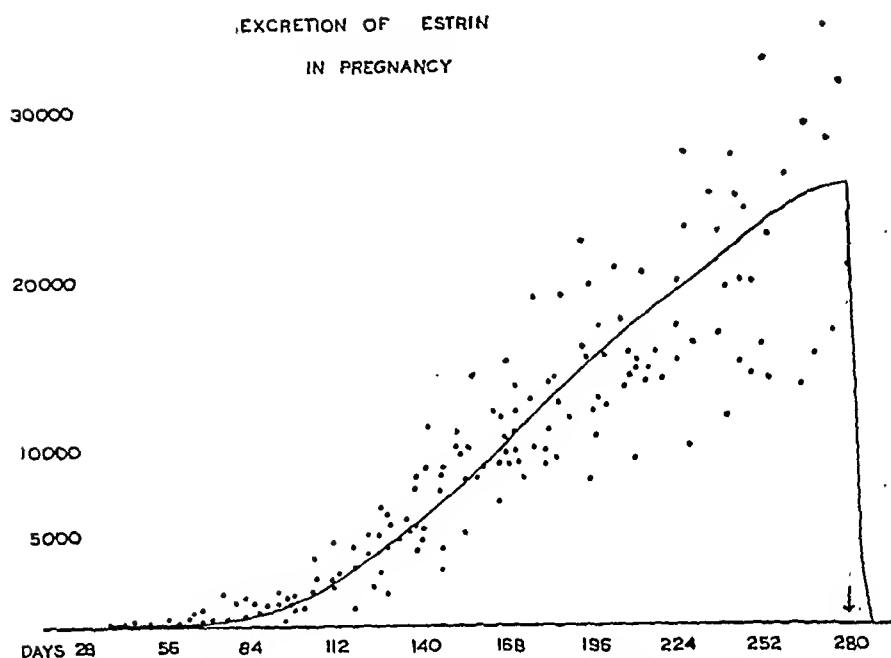


Fig. 2.—Excretion of total estrogens in the urine of 8 patients with normal pregnancy. The values are expressed in gamma excreted per twenty-four hours. Those under about 500 gamma are determined by biologic assay, those above this figure by a colorimetric method.

100 mg/24 hrs.  
Pregnanediol

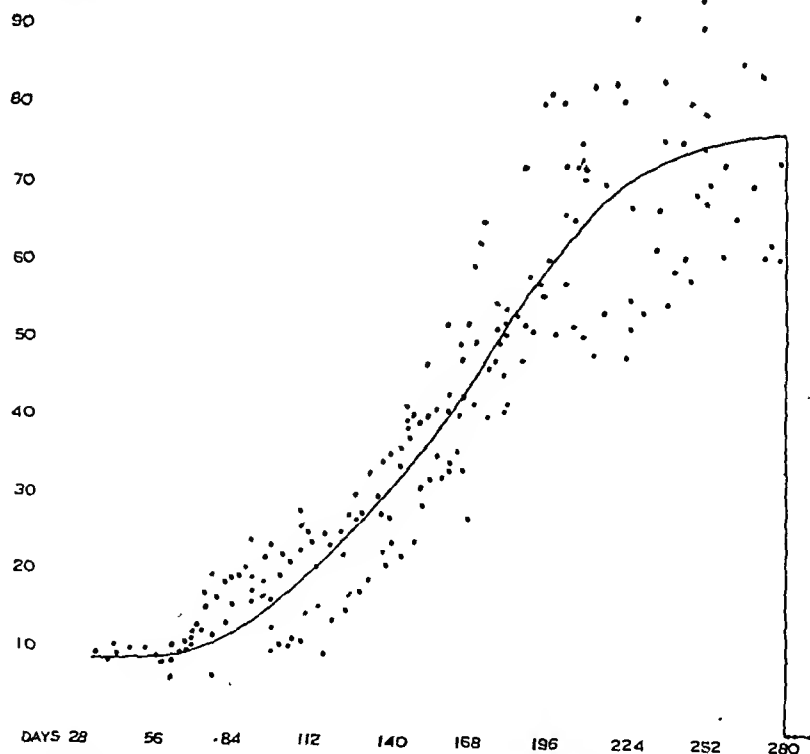


Fig. 3.—Excretion of pregnandiol in the urine of 8 patients with normal pregnancy.

pregnandiol in the presence of blood, it may be stated that when the amount of pregnandiol present is below 4 or 5 mg., the presence of blood in the specimen tends to obscure the final identification of the complex. In the figures, Curve 1 represents prolan excretion, Curve 2 pregnandiol excretion, and Curve 3 that of total estrogens.

### REPORT OF CASES

The cases will be divided into three groups. The first group comprises those patients in whom abortion actually occurred, the second those showing symptoms of threatened abortion, but in whom the gestation continued (these cases may or may not have had miscar-

#### CASE 14

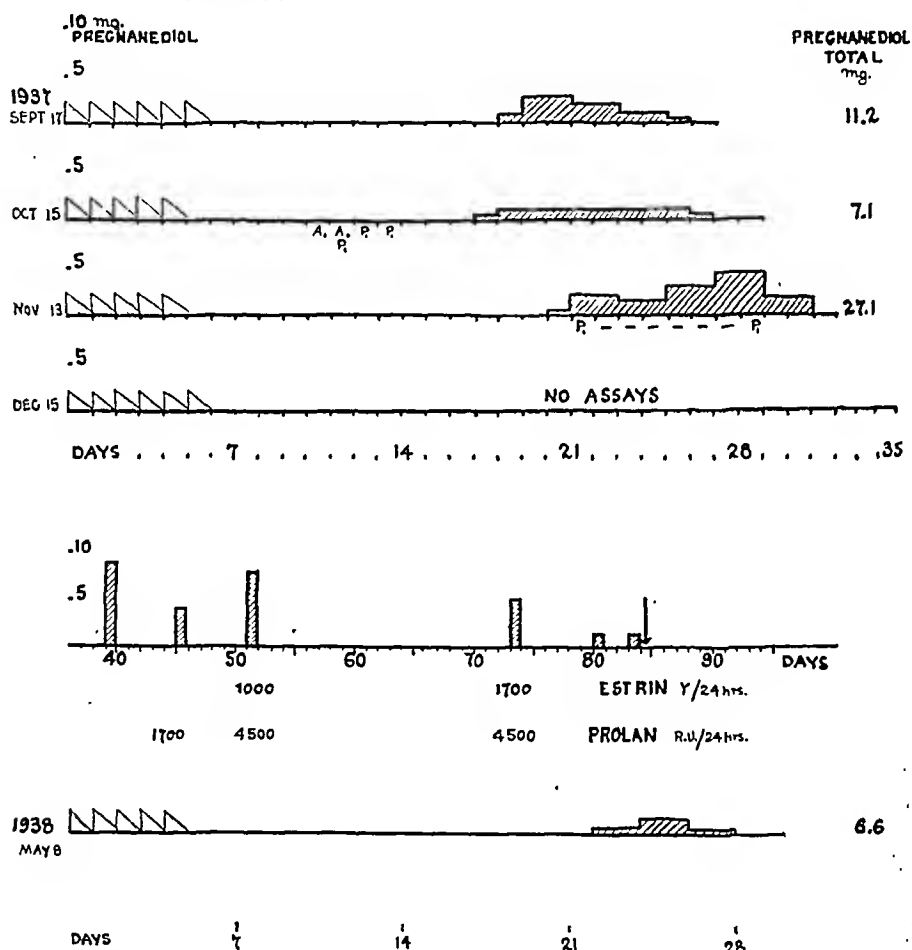


Fig. 4.—Pregnandiol, estrogen, and prolan excretion during the menstrual cycle and early pregnancy. Serrated areas represent days of menstruation. Shaded areas represent pregnandiol excretion. *P*, represents the injection of 100 M. U. of physex (pregnancy urine gonadotrophic extract) and *A* of 100 M. U. of antex (pregnant mare's serum gonadotrophic extract). The arrow marks the day on which abortion occurred.

riages in previous pregnancies), and the third those who had had one or more previous miscarriages, but who showed no abnormal symptoms during the pregnancy under investigation. The results of the assays in the first group are presented in Table II and Figs. 4 and 5. Case reports are given in detail where these are of particular interest,

until the hundredth day without any abnormal symptoms manifesting themselves. This rise is interpreted as due to the beginning of secretion of progesterone by the placenta. A few cases in which the ovaries have been removed earlier than the seventieth day and pregnancy has continued, make it probable that in some cases the placenta may begin to secrete earlier than this time. The rate of secretion of progesterone by the placenta gradually increases after this time up to term. The amount secreted varies in different individuals and in the same individual in consecutive pregnancies. It may depend upon the mass of placental tissue. There seems to be no significant change in progesterone metabolism immediately before labor, but progesterone ceases to be formed when the placenta separates, and its excretion product disappears from the urine shortly after this. The chorion is the source of prolactin from conception to term. In the first part of pregnancy estrogens and progesterone are formed in the ovary. At a varying time, but usually from the seventieth to ninetieth day, the placenta begins to secrete these substances. In most cases the corpus luteum ceases to function shortly after this. The placenta continues to form these substances in gradually increasing amounts until term. There is a transfer of function from one site of formation of progesterone and estrogens to another occurring usually in the third month. The cases presented below will illustrate the significance of this conception for the mechanism of the causation of abortion.

#### METHODS

Twenty-four-hour specimens of urine were collected, a few drops of tricresol were placed in the containers as preservative. In connection with the collection of twenty-four-hour specimens, it is naturally very important to be sure of the completeness of collection. In collecting specimens of urine over prolonged periods of time from the same patients, it has generally been found that remarkably even results are obtained in the day-to-day excretion of pregnandiol. It is only fair to state, however, that some of the fluctuations seen in the figures may be due to faulty collection, particularly when as in the case of occasional specimens the patients had not been trained in the collection of the urine. It is important to keep the specimens cool and to do the determinations as soon as possible after collection, in view particularly of the tendency of pregnandiol glucuronide to be hydrolyzed to free pregnandiol. Care was taken as far as possible to prevent blood from contaminating the urine. Prolactin was assayed and extracted by the same method as that used by Browne and Venning,<sup>6</sup> the units are also the same and are expressed as rat units per twenty-four hours. Estrogens were extracted with ether after hydrolysis with zinc and hydrochloric acid (Smith and Smith) and assayed either on the immature twenty-one-day-old hooded rat or determined by the method of Venning and others,<sup>26</sup> depending upon the amount present. If the value was below 500  $\gamma$  per liter, it was repeated on the rat assay. The values below about 500  $\gamma$  in the tables and figures are therefore in rat units, those above are in gamma of total estrogens. The changes from one type of estrogen to another found to occur in pregnancy by Smith and Smith<sup>25</sup> will not affect the results obtained by the chemical method, since the amount of color developed from estrone, estriol and estradiol are approximately the same. Pregnan-  
diol was determined by the method of Venning.<sup>27, 28</sup> It should be emphasized that the values in this and other papers by the authors are expressed as milligrams of pregnandiol per twenty-four hours, not as milligrams of sodium pregnandiol glucuronide.

In all cases the time of pregnancy is reckoned from the first day of the last actually occurring menstrual period. In connection with the determination of

TABLE II.\* PATIENTS IN WHOM ABORTION OCCURRED

CASE	DAY	REMARKS	PREG- NANDIOL MG./ 24 HR.	TOTAL ESTROGENS R.U./24 HR. OR GAMMA	PROLAN R.U./24 HR.
1	67	Bl.++* Pain			
Aged 30	68	Bl.++ 5 mg. Pr.	0	-	300
Gravida i	69	Bl.++ 5 mg. Pr.	0	-	500
	70	Bl.++	0	-	650
2	77	Bl.+			
Aged 26	84	Bl.++	-	-	55
Gravida vi	87-88	Bl.++			
	90		0	120	45
	93		0	330	120
	96	D. & C.			
3	81	Pain			
Aged 26	82	Bl.++ 5 mg. Pr.	-	-	<500
Gravida i	83	D. & C.	0	-	830
4	53		19.9	3340x	4500
Aged 38	56		17.3	3060x	1100
Gravida iii	57		15.6	3325x	3200
Para 0	63		11.0	2520x	2300
	66		5.9	2940x	1750
	67	Bl.+			
	68	Bl.+ 5 mg. Pr.	6.4	1600x	500
	69	Bl.+ 5 mg. Pr.	6.1	1750x	700
	70	5 mg. Pr.	0	900x	<83
	71	D. & C.			
7	80-90	Bl.+			
Aged 24	123	Bl.++			
Gravida i	132		-	17	4400
	137	Pain Bl.++ Ab.			
8	215		6.5	640	8800
Aged 40	218		4.9	300	1700
Gravida vi	219		6.2	900	4200
Para v	220-221		3.8	600	3000
	222		0.0	500	1570
9	100	Pain. Bl.+++			
Aged 28	100-106	Bl.++			
Gravida iii	107	Pain. Bl.++			
Para ii	107-127	Bl.+			
	120	Bl.+	26.2	3800x	5000
	124		25.8	2600x	-
	128	Fetus Ab.			
	140	D. & C.			
10	92	Bl.++			
Aged 30	101	Bl.+			
Gravida i	102	Bl.++			
	103	5 mg. Pr.			
	104	15 mg. Pr.			
	105	10 mg. Pr.			
	105-106		4.2	710x	2800
	107-108		5.3	900x	8300
	115		0	-	660
	146		-	-	1000
	155	D. & C.			

otherwise in the interests of conserving space the essential facts are given in the tables or in the legends to figures.

*Group I.*—Patients in whom abortion actually occurred. The results of the assays in Cases 1 to 11 are shown in Table II.

CASE 4.—F. C., aged 38 years, married 8 years, gravida iii, para 0, had had an exophthalmic goiter removed in 1936, had an adolescent goiter as child, and miscarried at three months, February, 1936, at the seventy-first day in 1937, and at the seventy-first day in 1938. Progesterone was given in the last two pregnancies.

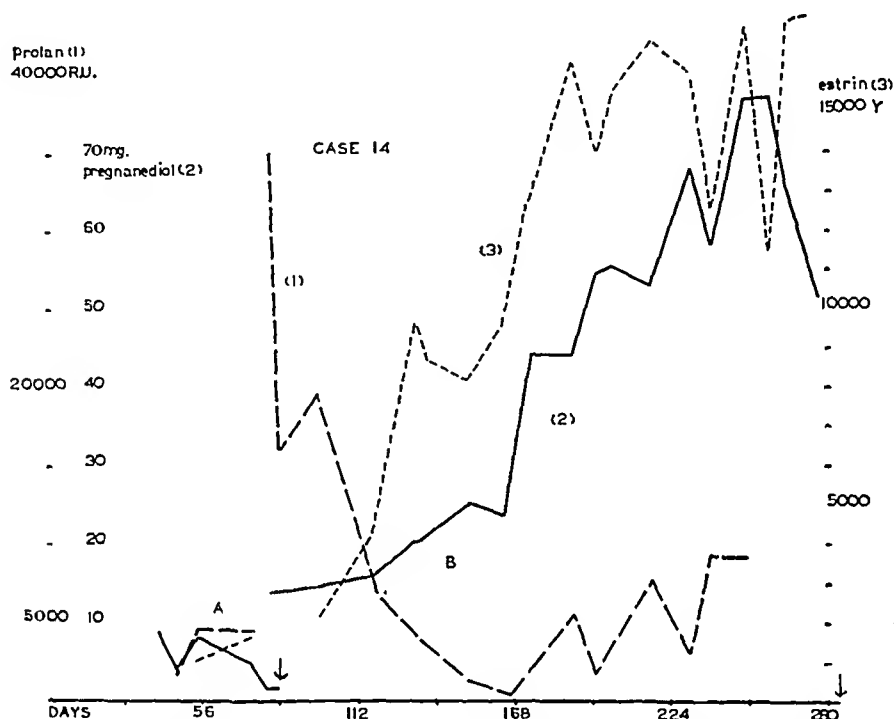


Fig. 5.—Pregnanediol, estrogen, and prolactin excretion in the same patient case as in Fig. 4. A, is the first pregnancy shown also in Fig. 4, which ended in abortion and B, is the second pregnancy which was normal throughout. In this and subsequent figures, Curve 1 represents the excretion of prolactin, Curve 2 of pregnandiol, and Curve 3 of total estrogens. The arrow marks the day on which parturition occurred, and each division on the horizontal axis is twenty-eight days.

Assays were begun in this case before symptoms commenced on the basis of the previous history. The assays showed a steady decline in pregnandiol excretion from 19.9 mg. per twenty-four hours on the fifty-third day to zero excretion on the seventieth day. The estrogen excretion was also higher than usual on the fifty-first day and declined towards the end. The prolactin was abnormally low even at the fifty-first day and fell to 500 R.U. per twenty-four hours two days after bleeding began. The value of 19.9 mg. of pregnandiol is unusually high for the period of pregnancy. This patient was found subsequently to excrete a total of 86 to 111 mg. of pregnandiol over eleven to thirteen days during the corpus luteum phase of the menstrual cycle; the highest twenty-four-hour excretion was 14.4 mg. This is an unusually high value and explains the high figure recorded here during early pregnancy.

CASE 7.—H. G., aged 24 years, had her last menstrual period on May 25, 1936. There was slight bleeding about the middle of August, that is about the eightieth or ninetieth day. There were no further symptoms until the one hundred and twenty-third day when vaginal bleeding began again. The uterus was found to be the



had German measles with high fever. On March 14 (ninety-second day) she bled enough to soil two pads and had spotted once before since having the measles, date unknown. On March 23 (one hundred and first day) there was spotting, a rather profuse flow on March 24, and she was admitted on March 25 (one hundred and third day). The uterus was the size of a three and one-half months' pregnancy. On the one hundred and third day 5 mg. of progesterone, one hundred and fourth day 15 mg., and one hundred and fifth day 10 mg. was given. She was discharged on April 3 (one hundred and twelfth day); and there has been no further bleeding. She was readmitted on May 16 (one hundred and fifty-fifth day); uterus was the size of a two and one-half or three months' pregnancy. A curettage was done on May 17. *Pathologic Report*: "Blood clot fibrin and young enmeshed ghosts of placental villi." No fetus was seen either at operation or histologic examination. Pregnanadiol and estrin excretion was low for the period of pregnancy and on the one hundred and fifteenth day the pregnanadiol fell to zero. The gonadotrophic output was, however, within normal limits for the period of pregnancy with the exception of the one hundred and fifteenth day. How much of the pregnanadiol excreted in the assay of the pooled specimens of the one hundred and fifth and one hundred and sixth days was due to the 10 mg. of progesterone injected on the one hundred and fifth day is difficult to determine. We have seen in previous cases that 5 mg. failed to cause any excretion. Injected progesterone is rapidly excreted as pregnanadiol under favorable circumstances and generally its effect on pregnanadiol excretion is all over within twenty-four hours. It is thus unlikely that the excretion on the one hundred and seventh and one hundred and eighth days was derived from this injected progesterone.

CASE 11.—H., aged 38 years, married 20 years, gravida v, para iii, miscarriage in 1937, last menstrual period April 25, 1938, was admitted Oct. 12, 1938 (one hundred and seventy-first day). Fetal movements had been absent since October 2. She was discharged on Oct. 19, 1938 (one hundred and seventy-eighth day), and readmitted on October 19, after having bled about half a pint at home. Labor was induced October 29 by gauze pack, and she delivered on October 31 (one hundred and ninetieth day). Hemorrhage and shock occurred after delivery.

The output of pregnanadiol was grossly low for the period of pregnancy, but was maintained at that low level right up to the time of delivery of the dead fetus. The total estrogen was grossly low, tending to rise slightly in the last two days. The prolactin was also low unlike the other cases of abortion at this period of pregnancy.

CASE 14.—Patient, aged 23 years, married one year, had had no previous pregnancies. There was some tendency to overweight. She took thyroid from time to time for a number of years. Basal rate was -6 per cent; blood cholesterol 156 mg. per cent. Menstrual periods were regular twenty-eight to thirty days, last menstrual period occurring on Dec. 14, 1937. No abnormal symptoms until March 8 (eighty-fifth day) when there was sudden profuse bleeding and abdominal cramps. Curettage was done on March 9. The histologic section showed subinvolved necrotic decidua. No villi were seen. A second pregnancy was entirely normal throughout with the exception of slight nausea in the first few weeks. Last menstrual period occurred on July 8, 1938. Spontaneous delivery took place on the two hundred and eighty-third day. The child was normal. The results of the assays during the menstrual cycle and through the first and second pregnancies are presented in Figs. 4 and 5. They will be discussed in detail later.

*Group II.*—Cases showing symptoms of threatened abortion but in whom the gestation continued.

CASE 12.—L. E. H. (Fig. 6), aged 34 years, married in 1927. *First pregnancy*: last menstrual period occurred on July 20, 1936; miscarriage at sixty-two days. *Second pregnancy*: Last menstrual period occurred on Oct. 4, 1937. First abnormal symptom was bleeding on November 5 (thirty-third day); bleeding continued slightly until November 17 (forty-fifth day) with small clots on the day when she was admitted to the hospital. Bleeding still continued and on November 20 (forty-eighth

TABLE II—CONT'D

CASE	DAY	REMARKS	PREG- NANDIOL	TOTAL ESTROGENS	PROLAN
			MG./ 24 HR.	R.U./24 HR. OR GAMMA	R.U./24 HR.
11	176		2.5	550	-
Aged 38	177	Bl.+++	4.2	200	170
Gravida vi	185		5.3	400	112
Para ii	186		5.3	500	112
	187		4.7	500	165
	188		4.9	1900	158
	189		4.9	1900	158
	190	Ab.			

\*Days are counted from the first day of the last menstrual period. The significance of the symbols is as follows: *Bl.*+, slight, *Bl.*++, moderate, and *Bl.*+++ profuse vaginal bleeding; *Pr.*, progesterone; *Op.*, operation; *Ab.*, passage of products of gestation; *D.* and *C.*, dilatation and curettage;  $\alpha$ , indicates that the estrogens were done by the chemical method and are expressed in gamma, the other estrogen values are in rat units.

size of a two and one-half months' pregnancy. On the one hundred and thirty-seventh day there were cramplike pains in the abdomen. The amniotic sac contained 150 c.c. of bloody fluid; there was no embryo visible. The placenta was 10 cm. in diameter and showed necrotic changes. The assays showed a normal gonadotrophic titer for the period of pregnancy, but there was practically no estrin.

CASE 8.—A. F., aged 40 years, gravida vi, para v, one miscarriage, had been married fourteen years. Two years ago she had two months' amenorrhea; menses returned uneventfully at that time. She was admitted to the hospital Oct. 14, 1938, on the two hundred and nineteenth day. No bleeding or pain had occurred. On examination the breasts were full and a pelvic mass the size of a five months' pregnancy was felt. There was no uterine souffle, and no fetal heart sounds were heard. The pregnandiol excretion was abnormally low and fell to zero on the two hundred and twenty-second day. Estrin was also abnormally low, but the gonadotrophic titer was within normal limits. The patient did not have any abnormal symptoms in hospital; she left the hospital, and it has not been possible to learn her subsequent history. This is almost certainly, however, a case of missed abortion.

CASE 9.—H., aged 28 years, gravida iii, para ii, had her last menstrual period on Sept. 14, 1937. On the one hundredth day (December 22) severe abdominal pain and a sudden profuse discharge of blood and watery fluid from the vagina. Bleeding continued intermittently from then on, but there was no further pain until the one hundred and seventh day when it was severe. On examination the cervix was large and edematous and admitted the tip of one index finger. Uterus was the size of a four months' pregnancy. A medical induction was ordered. On the one hundred and twenty-sixth day (January 16) the patient developed a severe pharyngitis and bronchitis with a fever of 104° F. On the one hundred and twenty-eighth day the fetal cord was found prolapsed and necrotic, the fetal body was passed and the head a day later. The placenta was, however, retained for twelve more days until the one hundred and fortieth day, when it was decided to strip it off after dilatation of the cervix.

Histologic examination showed hyalinization and infarction of the placenta. The pregnandiol, estrin, and gonadotrophic excretion values done on the one hundred and twentieth and one hundred and twenty-fourth days, that is a few days before delivery of a macerated fetus, were within the normal limits for this period of pregnancy. It seems fairly certain from the history of this case that the abortion was induced.

CASE 10.—J. M., aged 30 years, married two years, had had no previous pregnancy. Her last menstrual period was on Dec. 13, 1936. Early in March she had

forty-ninth days is excluded, which the authors feel can safely be done, then this case shows that a single determination showing low or even negative values, does not necessarily mean that the gestation has perished. We have seen that in the first group such low values do usually occur at this period of pregnancy in patients in whom abortion actually occurs, and in most instances do signify that the gestation is dying, particularly if they remain low on more than one determination.

CASE 13.—H. G. (Fig. 6), aged 28 years, married, gravida ii, para 0, had a miscarriage at about  $3\frac{1}{2}$  months two years ago. Her last menstrual period occurred on July 14, 1938. She had had severe nausea and vomiting since early in pregnancy. On September 5 (fifty-first day) there was very scanty uterine bleeding. Treatment upon admission consisted of fluids intravenously; diet. Progesterone was

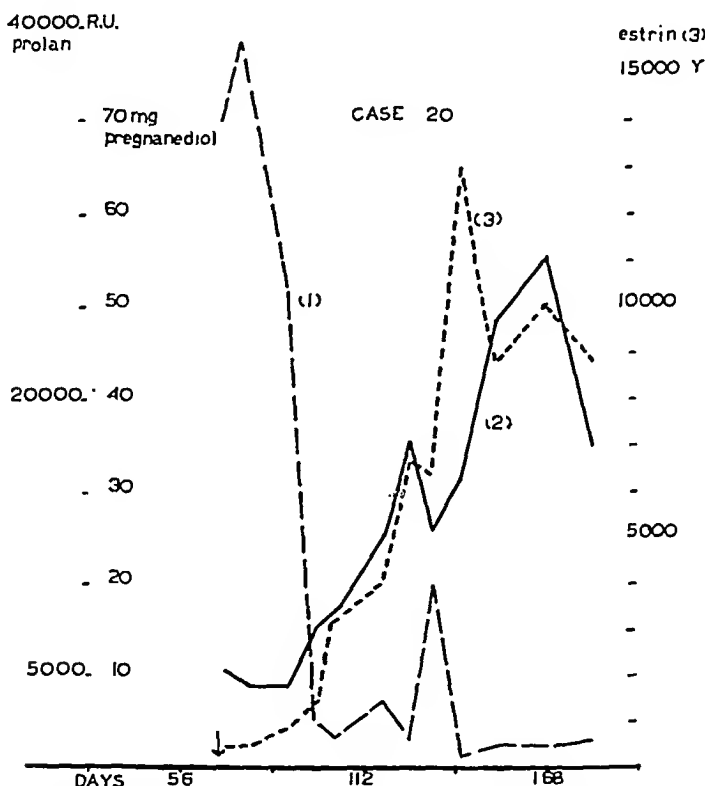


Fig. 7.—Case 20: Patient had had one previous missed abortion, with slight bleeding on the sixty-ninth day only. There were no further symptoms. Assays were normal throughout. No progesterone was given.

given, beginning with 4 mg. on date of admission (fifty-first day) and continuing with 5 mg. each day up to and including September 17 (sixty-third day). Her condition improved slowly, and she was discharged by ambulance September 23 (sixty-ninth day). There was no further bleeding, and she delivered a normal child on April 20, two hundred and seventy-ninth day. The results are shown in Fig. 6.

On the fifty-second day the pregnandiol was 2.3 mg., an abnormally low value, in spite of the injections of 5 mg. of progesterone mentioned above. The rate of excretion was between 5 and 8 mg. from the fifty-third to the fifty-eighth day, rising to 15.0 mg. on the fifty-ninth and sixtieth days, and falling to 8.0 mg. on the sixty-first day. It declined further to 5 or 6 mg. on the sixty-fourth day after the cessation of the progesterone injections. On the seventy-third day, in view of the decrease in pregnandiol to 4.1 mg. on the sixty-eighth day, 5 mg. of progesterone were given and repeated on the seventy-fourth, seventy-fifth, seventy-seventh, eighty-ninth, and ninety-first days. The fall in pregnandiol was only temporary, however, and it

day), she was taken to the operating room. As no bleeding had occurred that morning, however, the curettage was postponed. No further bleeding occurred and the patient was sent home on December 1 (sixtieth day). She remained in bed until early in February, 1938, when it seemed from the assays that the pregnancy was progressing normally. She delivered a normal child spontaneously on the two hundred and ninety-first day. She received no progesterone at any time. The results of the assays in this case are shown in Fig. 6.

Assays were begun on the fortieth day, that is, after bleeding had been going on for a week. At this time, the pregnandiol was 11.3 mg., estrin 340 R. U., and prolan 850 R. U. per twenty-four hours. The first two values are normal, the last is low. However, on the forty-second day the prolan had risen to 14,520 units, which is normal. The pregnandiol decreased to 2.9 mg. on the forty-seventh day and to zero

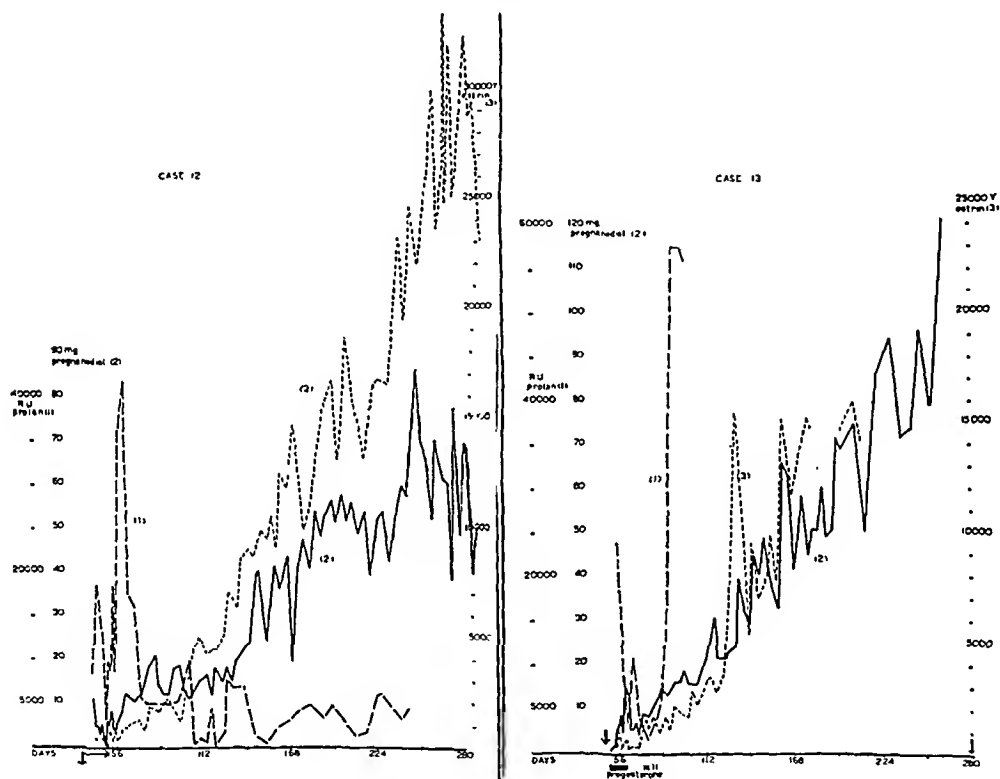


FIG. 6.—Two cases of threatened abortion. One patient had a previous miscarriage on the sixty-second day. *Case 12:* Patient had slight bleeding on the thirty-third to forty-eighth days. Thereafter there were no abnormal symptoms. Pregnanndiol, estrin, and prolan fell to abnormally low levels on the forty-seventh to forty-eighth days. No progesterone was given. *Case 13:* Patient had one miscarriage at three and one-half months, and slight bleeding on the fifty-first day. Five milligrams of progesterone were given from the fifty-first to the sixty-third days. There were no further symptoms. Arrows represent the time at which bleeding occurred.

on the forty-ninth day; the estrin was zero on the forty-eighth day and the prolan less than 420 units on the forty-eighth and forty-ninth days. These assays gave the impression that the gestation had perished. On the fiftieth day, however, the pregnandiol was 6.0 mg., the estrin 700 units, and the prolan 10,000 units. Thereafter the prolan rose to the usual peak at fifty-six days, and then decreased in a normal manner and remained within normal limits throughout the rest of the pregnancy. The estrin excretion rate rose in a normal manner, a rather more rapid rise beginning about the ninety-fourth day. The pregnandiol rose to a level of between 10 and 20 mg. at about the sixtieth day and began to rise further from that level about the one hundred and thirty-fifth day. Both estrin and pregnandiol curves were within normal limits after this, the pregnandiol curve showing some fluctuations. If the possibility of confusion of specimens with some other patient on the forty-eighth and

CASE 28.—Fa., aged 30 years, married seven years, gravida ii, para 0, had her last miscarriage in 1936 at three months, preceded by brownish discharge. Her last menstrual period was on Jan. 24, 1939. The first abnormal symptom appeared on the forty-first day, consisting of brownish discharge. She was put to bed, and was given 5 mg. of progesterone daily from the forty-second day to the forty-fifth day and every other day from then until the fifty-eighth day. No further bleeding occurred after the forty-eighth day.

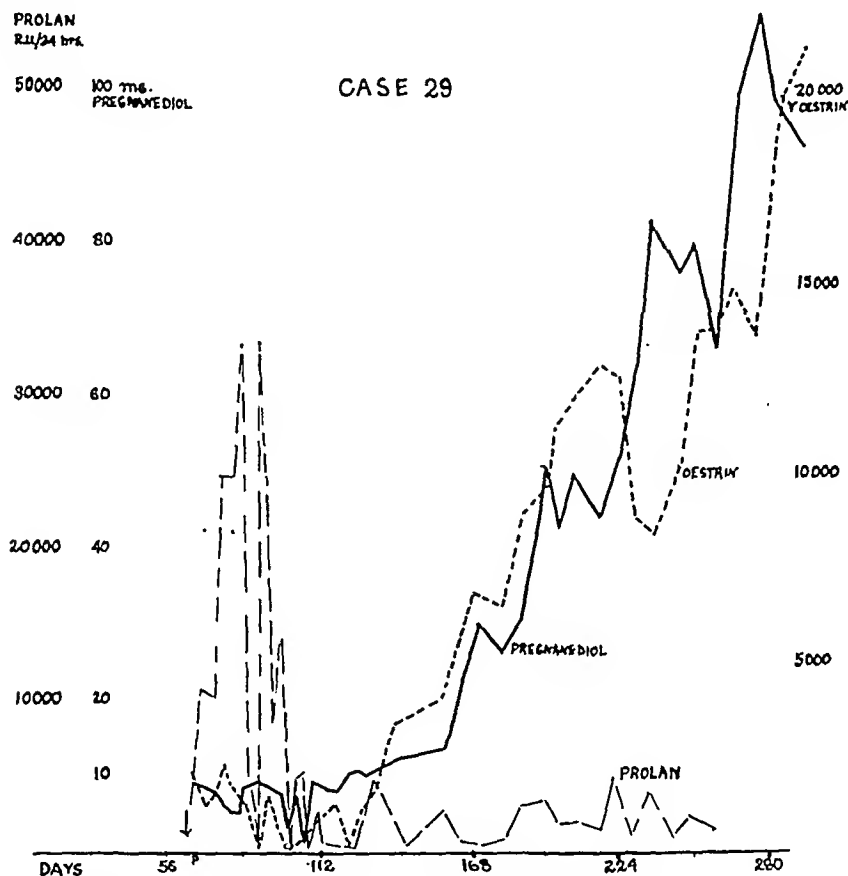


Fig. 8.—Case 29: Patient had had two previous miscarriages, one in the second month and one in the third month. There was slight bleeding on the sixty-ninth and seventieth days. Five milligrams of progesterone were given on the seventy-first and seventy-second days and vitamin E thereafter. She was kept in bed until about the one hundred seventy-fifth day. There were no further abnormal symptoms. Pregnanediol and estrin values fell to abnormally low values about the one hundred twelfth day. Up to about the one hundred fiftieth day, the pregnanediol excretion rose but slightly above the level of 10 mg. per twenty-four hours. Thereafter it rose rapidly to high normal values. Estrogens began to rise about twenty-eight days before the rise in pregnanediol occurred.

The assay results are shown in Table III. The pregnanediol values are perhaps a little low if one considers the daily injections of progesterone until about the fifty-seventh day; but the actual values are within normal limits. The estrogen values are normal and the prolan excretion shows a high peak from the forty-third to forty-sixth days and another high point about the sixtieth day. On the eighty-first day which is the last assay completed, the estrogen excretion is beginning to show the rise usually occurring at this time of pregnancy. There is nothing in these assays to differentiate them from those of a normal pregnancy.

CASE 29.—J. R. (Fig. 8), aged 32 years, married six years, gravida iii, para 0. *First pregnancy:* Miscarried in November, 1935, at about seven weeks. *Second pregnancy:* Last menstrual period on Aug. 16, 1936; first abnormal symptom bleed-

probably was unnecessary to give the progesterone. The pregnandiol excretion began to rise from this level about the seventy-ninth day, a normal time for the increase to occur, and rose steadily in a normal manner throughout. The total estrogens were perhaps a little low at first, but rose parallel to the pregnandiol with some fluctuations. The determinations in the latter part of pregnancy have not been completed. The prolan curve showed a high point of 30,000 units on the fifty-fourth day, then a series of lower values and a second rather unusually late peak of 50,000 units on the eighty-fifth, eighty-ninth, and ninety-third days.

CASE 20.—(Fig. 7.) Patient, aged 24 years, had a missed abortion in 1936. Symptoms began at the one hundred and sixty-fifth day when the uterus was the size of three or three and one-half months' pregnancy. *Second pregnancy:* Last menstrual period occurred on Sept. 8, 1937. She bled slightly on the sixty-ninth day, and there was no further bleeding. Labor occurred on the two hundred and eighty-first day, and the child was normal. The assay results are shown in Fig. 9.

The excretion rate of prolan, estrogens, and pregnandiol was normal throughout, except a slight decrease in excretion of pregnandiol and estrogens about the one hundred and eighty-second day. After this time no assays were done. Labor was normal and at term.

CASE 27.—Ea., aged 31 years, last menstrual period June 28, 1937, had slight bleeding in early August. On September 12 to 18 she passed a moderate amount of dark blood; there was no pain and no further symptoms. She delivered normally on the two hundred and seventy-seventh day. No progesterone was given. Assays given in Table III show normal values for pregnandiol and estrogens and a rather high value for prolan.

TABLE III. PATIENTS IN WHOM ABORTION THREATENED

CASE	DAY	REMARKS	PREGNANDIOL MG./24 HR.	TOTAL ESTROGENS R.U./24 HR. OR GAMMA	PROLAN R. U./24 HR.
27	76-82	Bl.+			
	88		15.9	1,050	83,000
	89		14.3	800	30,000
28	41	5 mg. Pr.			
	43	5 mg. Pr.	4.6	154	102,000
	44	5 mg. Pr.	4.6	154	102,000
	45	5 mg. Pr.	5.4	179	116,000
	46	-	5.4	179	116,000
	47	5 mg. Pr. Bl.+	4.4	150	24,000
	48	5 mg. Pr. Bl.+	4.4	150	24,000
	49	-	5.2	240	30,000
	50	5 mg. Pr.	5.2	240	30,000
	51	5 mg. Pr.			
	53	5 mg. Pr.			
	55	5 mg. Pr.			
	57	5 mg. Pr.	9.2	450	50,000
	58	5 mg. Pr.			
	60	5 mg. Pr.	9.3	450	110,000
	67	-	10.3	550	83,000
	71	-	7.7	550	
	78	-	11.5	830x	
	81	-	11.7	1,700x	
31	97	Pain	10.4	980x	11,000
	103		4.6	840x	-
	104		3.4	-	-
	106		7.0	1,870x	-
	108		8.5	2,840x	-
	128		14.6	4,400x	-

x. Indicates that the estrogens were done by the chemical method and are expressed in gamma; the other estrogen values are in rat units.

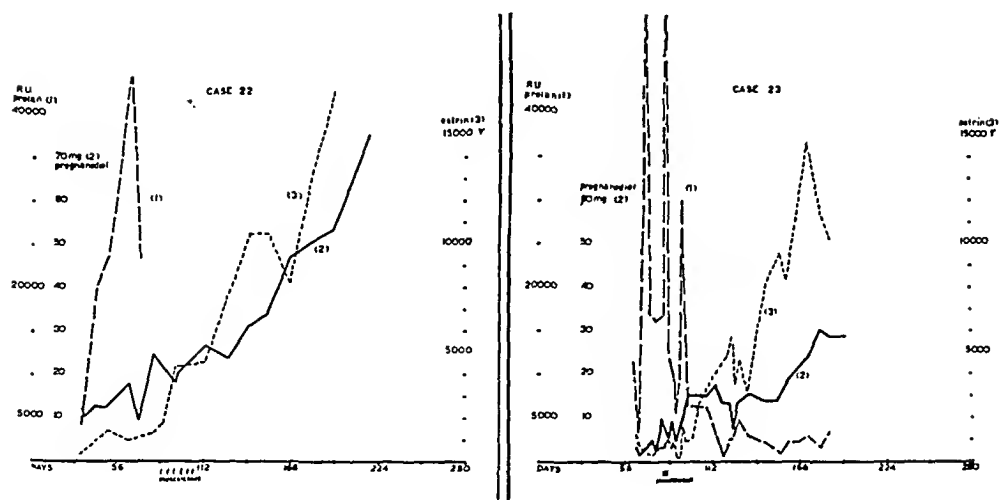


Fig. 9.—Case 22: Patient had had two previous miscarriages, one at six months (symptoms began at three months) and the second at three months. There were no abnormal symptoms during the present pregnancy. The assay values were normal throughout. The progesterone given in 5 mg. doses as indicated was probably unnecessary. Case 23: Patient had had two previous miscarriages at four months and at two months. There were no abnormal symptoms during the present pregnancy. Excretion of prolan and estrogens was normal, but pregnanediol was abnormally low in the early part of pregnancy and failed to rise to the normal level even at the one hundred eightieth day. Progesterone 9 mg. daily was given from the eighty-first to eighty-fourth day.

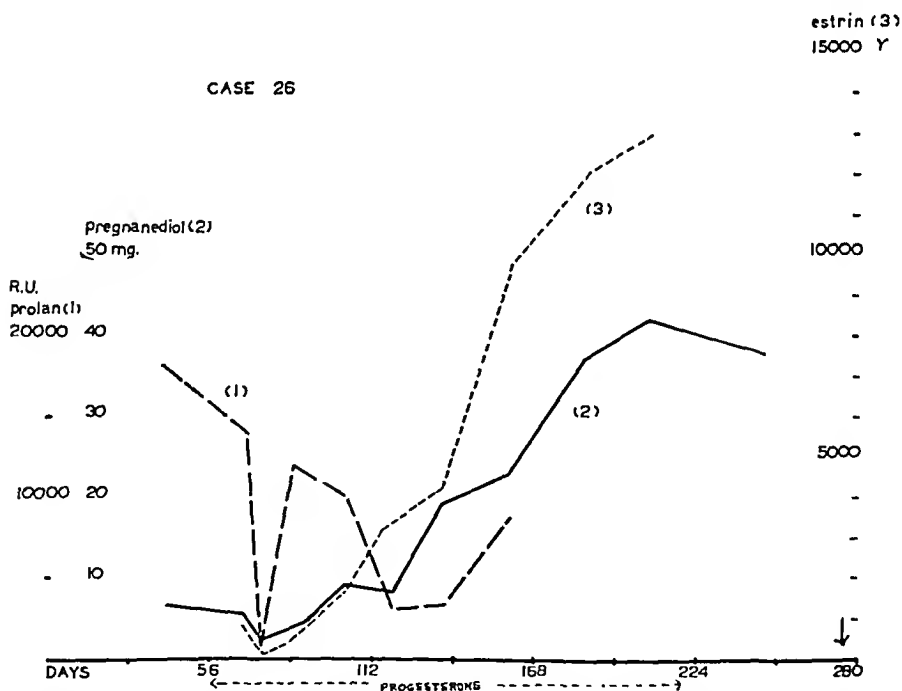


Fig. 10.—Case 26: Patient had had one previous miscarriage at three months. There were no abnormal symptoms in the present pregnancy. On the seventy-fourth day, 700 units of prolan and 2.3 mg. of pregnanediol were excreted. It was suspected that the gestation was dying, but the pregnancy continued normally and the excretion of estrogen began to rise about the one hundredth day and a definite rise in pregnanediol began about the one hundred and twelfth day; 1 mg. of progesterone was given three times weekly from the fifty-sixth to the one hundred eighteenth days and 1 mg. twice weekly from the one hundred and eighteenth to the two hundred and tenth days.

ing on October 31 (seventy-seventh day). She was admitted on November 1; 5 mg. of progesterone was given on November 2 and 3; on November 4 dilatation and curettage, no fetus was seen. *Pathologic report*: "Decidua compacta and spongiosa with few necrotic young villi." This was followed by acute endometritis with onset on November 16, twelve days postoperative. *Third pregnancy*: Last menstrual period Jan. 9, 1938 (approximately); slight spotting on February 4 (twenty-seventh day). There was slight bleeding on March 18 and 19 (sixty-ninth and seventieth days). She was admitted March 19, given 5 mg. of progesterone on March 20 and 21, and discharged on March 23. The patient was kept in bed until July, and given vitamin E (Horner). She was delivered Oct. 24, 1938 (294th day) of a normal child.

The prolan values were irregular in the first part of the pregnancy. Both estrogen and pregnandiol values fell to abnormally low values about the one hundredth day, though there were no symptoms at this time. The striking feature of the pregnandiol curve was the very late period at which it begins to rise above the level characteristic of early normal pregnancy. It was not until about the one hundred and fiftieth day that a significant rise occurred. After the one hundred and sixtieth day it was rapid and reached high normal values before the end of pregnancy. The rate of excretion of estrogens began to rise about twenty-eight days before that of pregnandiol, and also followed a normal course thereafter.

CASE 31.—Wi. had two miscarriages in 1935 at three months. Her last menstrual period occurred on Aug. 26, 1936. On the ninety-seventh to one hundred and tenth days there was pain in the back and abdomen, no bleeding, and the pregnancy proceeded normally to term. The prolan titer (Table III) on the ninety-eighth day was normal. Estrogen excretion was also normal. Pregnan diol excretion fell from 10.4 mg. on the ninety-seventh day to 3.4 mg. on the one hundred and fourth day and rose again to 14.6 mg. by the one hundred and twenty-eighth day. It is questionable whether this should be regarded as a threatened abortion.

*Group III.*—The third group of cases comprises those patients who had had one or more miscarriages in previous pregnancies, but who showed no abnormal symptoms during pregnancy under investigation.

CASE 22.—W. M. (Fig. 9) had had two previous miscarriages; one occurred in 1936 at six months; symptoms began at three months; the second miscarriage occurred at three months in 1937. *Third pregnancy*: Last menstrual period on Sept. 21, 1938. No abnormal symptoms had occurred during the present pregnancy. The assay values were normal throughout. Injections of 5 mg. of progesterone were given as indicated in the figure from the eighty-sixth to the one hundred and tenth day as a precautionary measure; but this was probably entirely unnecessary.

CASE 23.—U. (Fig. 9) had had one normal pregnancy, and also had had a miscarriage in 1935 at four months, and in 1937 at two months. Her last menstrual period occurred on Sept. 11, 1938. There were no abnormal symptoms. The excretion of prolan and estrogens was normal, but an unusually low amount of pregnandiol was excreted from the sixty-second day (when assays began) to the eightieth day (1.0-4.9 mg./24 hr.); 9 mg. of progesterone were given daily on the eighty-first to the eighty-fourth days; the level of pregnandiol rose slightly during the injections; a level of 13 to 15 mg. was maintained from the ninety-sixth to the one hundred and fifty-fourth day. After this the value rose to 30 mg. about the one hundred and eightieth day; it was still definitely lower than the usual normal value for this period of pregnancy.

CASE 26.—R. A. (Fig. 10) had had one previous miscarriage at three months. Her last menstrual period was Aug. 13, 1938. The prolan values around the sixtieth day are perhaps somewhat lower than normal, being 14,000 units. On the seventy-fourth day only 700 units were excreted, and the pregnandiol value dropped to 2.3 mg. from 5.2 mg. on the sixty-seventh day. At this time it was thought from the



repeating the assay on the eighty-third day, the pregnandiol had risen to 29.1 mg., which is a high normal value. Advice was given that no further progesterone was necessary.

CASE 33.—D. had had one miscarriage at the third month. Her last menstrual period occurred on July 27, 1928. The assays shown in Table IV are within normal limits. There were no abnormal symptoms during the pregnancy.

CASE 34.—J. had had previous miscarriages at the fifth and tenth weeks. Her last menstrual period occurred on Dec. 2, 1936. There were no abnormal symptoms in this pregnancy which proceeded normally to term. The assays shown in Table IV show a normal excretion of pregnandiol which begins to rise from the level of early pregnancy at the normal time. The prolan excretion was rather low for the fiftieth to sixtieth day.

CASE 35.—T., aged 29 years, married four years, had had one miscarriage in the third month. Her last menstrual period occurred on September 25, 1938. There were no abnormal symptoms. The assay values (Table IV) are essentially normal. The time of the rise in pregnandiol excretion above the level of 12 mg. is perhaps somewhat delayed. It does not begin until the one hundred and twenty-first day.

#### DISCUSSION

In the first group Cases 1 to 4 and Case 14 are spontaneously occurring abortions in the early part of pregnancy. In Cases 1 to 3 the assays were begun only after symptoms had occurred. The pregnandiol is negative in 3 cases and low in the fourth, and the prolan is abnormally low in all of them. In connection with the decision as to what is a normal prolan value, comparison should be made with the values set forth in Fig. 3 and Table I. From these it is obvious that what would be a normal level for prolan in the sixth month, for example, would be definitely abnormal in the late second and early third months when the normal high peak of excretion occurs. In Case 6 the assays were done eight days before the actual abortion which may account for pregnandiol still being present. In Case 4 assays were started fourteen days before the onset of symptoms and at that time showed a low prolan with high estrin and pregnandiol. These high values are explained, as has been mentioned, by the character of the corpus luteum in this individual. It secretes unusually large amounts of progesterone even in the menstrual cycle. Progesterone in 5 mg. doses, started after symptoms commenced, failed to influence the course of events. In these cases the gestation was obviously degenerated before the onset of symptoms. Case 14 may be discussed in more detail. In Fig. 4 are seen the assays of pregnandiol in the menstrual cycles; they are abnormally low, even the injection of pregnancy urine gonadotrophic extract fails to raise the excretion to the normal level. One may speculate as to the cause of abortion in this case. First, it is possible that the low pregnandiol excretion in the menstrual cycles was a reflection of an inadequate corpus luteum, that this indicated an abnormal follicle and so, conceivably an abnormal ovum. Second, the fertilized ovum may have been normal, but assuming that the corpus luteum in the cycle during which conception took place was as poorly functioning as in the other cycles, then satisfactory progestational

assays that the gestation had perished. However, on the one hundred and first day, the pregnandiol was 9.4 mg. and the prolans 10,000 R. U. and on the one hundred and thirty-fourth day the fetal heart was heard. The pregnandiol excretion rose to 19.3 mg. by the one hundred and thirty-seventh day and was about 40.0 mg. on the one hundred and eighty-fifth, two hundred and seventh, and two hundred and forty-eighth days, which is lower than usual. The total estrogen excretion was more or less normal throughout. One milligram of progesterone was given three times weekly from the fifty-sixth to the one hundred and eighteenth day, and 1 mg. twice weekly from the one hundred and eighteenth to the two hundred and tenth day. It is difficult to estimate the effect of this relatively small amount in preventing the occurrence of symptoms. Labor was induced on the two hundred and seventy-fourth day and a normal child was born.

CASE 32.—Co. had had several miscarriages on previous occasions at the third month. She was receiving 1 mg. of progesterone daily up to the seventy-fifth day. The assays were requested as a guide to the necessity for further therapy. As seen from Table IV, the assay values were normal for the period of pregnancy, and on

TABLE IV. PATIENTS IN WHOM ONE OF MORE PREVIOUS PREGNANCIES HAD TERMINATED IN ABORTION BUT WHO SHOWED NO ABNORMAL SYMPTOMS DURING THE PREGNANCY UNDER INVESTIGATION

CASE	DAY	REMARKS NUMBER OF MISCARRIAGES	PREGNANDIOL MG./24 HR.	TOTAL ESTROGENS R.U./24 HR. OR GAMMA	PROLAN R.U./24 HR.
32	75	Several	16.3	555	71,500
	83		29.1	600	--
33	63	1	18.3	--	64,800
	87		25.6	1,500x	28,220
	100		28.5	1,330x	22,100
34	51	2	8.8	--	5,500
	56		9.1	--	6,600
	72		17.6	655	2,200
	89		19.4	--	--
	125		28.0	--	3,000
35	40	1	7.8	840	1,150
	50		10.1	1,980	15,000
	57		10.1	1,105x	17,400
	65		11.0	1,400x	112,000
	72		11.6	1,140x	63,000
	78		13.5	3,020x	41,000
	85		11.3	1,990x	14,600
	88		14.7	1,170x	32,400
	93		12.2	2,465x	8,000
	100		12.3	1,760x	9,000
	106		12.2	3,220x	
	114		13.0	1,920x	6,000
	121		17.7		2,950
	127		20.8		
	135		26.8		1,700
	141		25.8	9,110x	
	155		28.4		8,525
	163		41.6		2,420
	169		49.6		11,880
	177		45.3		
	183		58.8		
	191		58.0		
	198		70.1		
	205		82.4		

x. Indicates that the estrogens were done by the chemical method and are expressed in gamma, the other estrogen values are in rat units.

mechanism, etc., may affect excretion of pregnandiol even when progesterone is being produced, so that a negative pregnandiol does not necessarily mean absence of progesterone from the body. Numerous other cases have been reported in which the corpus luteum has been removed at or before this period of pregnancy and the pregnancy has carried to term.

Case 8 is of interest since it presents the findings in a case of induced abortion. In this case in spite of the bleeding, the assay values are entirely normal for the period of pregnancy. Four days after the last assay the fetus was delivered in a macerated condition, but it will be noted that the placenta remained firmly attached and had to be removed sixteen days after the last assay. This shows clearly that the fetus is not the source of the hormones excreted in the urine, more particularly that the fetal adrenal is not the source of the pregnandiol. It also illustrates that if a gestation has developed normally and the fetus is killed by outside interference the placenta continues to function at least for a time. This is unlike those cases in which the death of the fetus is due to an abnormality which affects both fetus and placenta. Frank,<sup>29</sup> in an intrauterine full-term pregnancy in which the placenta had been left for eighteen days after delivery, found the blood estrin still high, and Ware and Main,<sup>30</sup> in an intra-abdominal pregnancy at term, found that prolactin persisted in the urine for about a month.

Cases 7, 8, 10, and 11 are missed abortions occurring later in pregnancy. The striking feature in them (except in Case 11) is that the prolactin values are entirely normal for the period of pregnancy, unlike the cases of abortion completed early. The excretion of pregnandiol and estrogens on the other hand is grossly low. In Case 7 the gestation ceased to develop presumably at the time of the first symptom (eighty to ninety days), in Case 8 the time of cessation of development is unknown but was probably after the fifth month, in Case 10 probably at the time of the first symptoms at the one hundred and fifth day, and in Case 11 possibly on the one hundred and sixty-first day. On this basis then the assays were done in Case 7 about fifty days, in Case 8 about two months, in Case 10 at the time and ten and forty days, and in Case 11, fifteen to thirty-eight days after the cessation of development of the gestation. The assay findings probably depend upon the time in pregnancy at which the gestation ceased to develop and the length of time which had elapsed before assays were done as well as upon the degree of degeneration which had occurred in the placenta. It may be said that the placenta (chorion) begins to form prolactin before it begins to form estrogens and progesterone. If the gestation ceases to develop before the placenta has begun to form these substances to any extent as in Cases 7 and 10, then apparently it seems not to go on to develop that function, or if it does, loses it before the time of assay in these cases, even though it remains in contact with the maternal circulation and continues to secrete prolactin. If as in Cases 8 and 11 cessation of development occurs later in pregnancy, assuming that they were normal up to that time, the placenta

transformation of the endometrium may have failed to take place, so that while the ovum did implant it failed to develop normally. It will be seen that in the early part of the gestation (forty to fifty days) the pregnandiol excretion was normal. The prolactin excretion, however, failed to rise, remaining at 4,500 units. This may reflect the failure of the chorion to develop normally in an abnormal gestation due to either of the above causes or to any other cause. In this connection one may compare the case of ectopic gestation previously reported in which a fall of urinary prolactin excretion took place with each new hemorrhage into the gestation sac.<sup>6</sup> Since we have seen that as the corpus luteum grows older it probably needs increasing gonadotrophic substance to keep it functioning, after about the seventy-fifth day in this case the 4,500 units failed to maintain the corpus luteum and it began to degenerate as shown by the decrease in pregnandiol excretion, and abortion occurred. This case illustrates clearly the course of a gestation, which from the prolactin excretion and the histological findings at the time of abortion, failed to develop normally from a very early stage, though symptoms did not occur until much later. The onset of symptoms may be determined by the endocrine relations described above. It is obviously futile to treat such a case with progesterone or anything else at the time the symptoms appear. On the second hypothesis advanced above it might have done some good to treat the patient with progesterone during the luteal phase of the menstrual cycle, but this is hardly practicable. After the first pregnancy another assay in the menstrual cycle showed the same low findings. The second pregnancy (Fig. 5, B) proceeded entirely normally; whether this was due to the occurrence at intervals of a normal corpus luteum in this individual, which would provide an adequate implantation site and would persist long enough for the placenta to take over the formation of progesterone, or to the existence of a normal fertilized ovum in the second pregnancy is purely speculative. In Case 4 one would have to assume a faulty germ plasma reflecting itself in a poorly developed chorion which produced an amount of prolactin inadequate to maintain the corpus luteum, since in this case the pregnandiol and estrin excretion were high. The fifth case, not reported in detail here, illustrates the effect of removal of the corpus luteum at the fifty-second day of gestation. Four days later pregnandiol was negative and the prolactin was definitely low, falling to 55 units ten days after the operation and abortion followed. In the case of Jones and Weil,<sup>24</sup> the patient was operated upon at the fifty-eighth day and pregnandiol persisted for three days postoperatively; on the fifth to twelfth day it was negative, and then reappeared and by the one hundred and thirty-sixth day of pregnancy had reached a normal level and pregnancy continued to term. This negative period indicates according to these authors that pregnancy may persist at least for a short time without progesterone or at least with minimal amounts. This is of interest in view of the temporarily negative finding in a case of threatened abortion reported in this paper. On the other hand we know that factors such as the glucuronic acid conjugation

others with normal or temporarily slightly low pregnandiol and normal estrogens and prolan in whom symptoms occurred and who carried to term.

In Table IV are shown 4 patients who had miscarried in previous pregnancies. Only one (Case 32) received progesterone in 1 mg. doses up to the seventy-fifth day. All showed entirely normal assay values with the rise in pregnandiol excretion occurring at the usual time. The patient in Case 26 had had one previous abortion and showed no symptoms in the present pregnancy. In spite of this the pregnandiol and prolan assays were very low at the seventy-fourth day and the rise in pregnandiol began a little late, and remained low throughout the rest of pregnancy. Case 22 and 23 are both patients who had had two previous miscarriages; in the patient in Case 22 the values were entirely normal throughout, and the progesterone was almost certainly unnecessary. In Case 23 the pregnandiol values were low and the rise in pregnandiol delayed.

There are then some patients who have aborted in a previous pregnancy or pregnancies, including cases of repeated or habitual abortion, in whom a subsequent pregnancy may be entirely normal from all points of view. There are others who may or may not have symptoms in whom the pregnandiol assays and sometimes the prolan assays are low at the critical period of pregnancy and in whom the normal rise in pregnandiol excretion takes place later than usual and may fail to rise to the usual level late in pregnancy.

Based upon the considerations discussed in the introduction and upon the findings in the cases reported here, the following theory of the endocrine mechanism of threatened and habitual abortion may be outlined. It has been previously discussed by Browne and Venning,<sup>6</sup> and parts of it have been suggested by many investigators. Experimental evidence with regard to the metabolism of progesterone in human pregnancy has, however, been lacking hitherto, and consequently the theory has lacked basis.

As stated in the introduction, the evidence suggests that there are two sources of progesterone and estrogens in pregnancy in the human being. These are the ovary with corpus luteum and the placenta. We interpret the rise in pregnandiol excretion which occurs about the seventieth to ninetieth days in most normal cases, as being due to the beginning of secretion of progesterone by the placenta. It was previously thought that, since the corpus luteum degenerates in many instances about the third month and since the ovaries could be removed and pregnancy continue, progesterone was unnecessary in the latter part of human pregnancy. This view is no longer tenable. Whether all the pregnandiol in late pregnancy is derived from progesterone and what is the minimum level necessary for maintenance of pregnancy is unknown. The time at which the transfer of function occurs from ovary to placenta varies in different individuals and in the same individual in different pregnancies. If, however, the corpus luteum ceases to produce progesterone for any length of time before the placenta begins to secrete it, abortion will follow. The time at

had by that time begun to form estrogens and progesterone and these substances continue to be excreted for some time though in smaller quantities than normal. In Cases 8 and 10 it is seen that pregnandiol may become negative in the urine without abortion occurring immediately, and in Case 11 abortion occurred while pregnandiol was still being excreted.

In the second group are included the cases of threatened abortion. It is in these cases that the difficulty of determining the effect of various forms of therapy arises. In this and the next group are included cases which fall into the class of habitual abortion. We shall limit ourselves here to discussion of the endocrine factors which we believe to be involved in the causation of symptoms in these cases, clearly recognizing, however, that there may be numerous other factors operating. We believe that the endocrine factors are in many instances the final common pathway upon which these other influences exert their effect.

Cases 12 and 13 (Fig. 6) may be compared; both patients had had one previous miscarriage, both had slight symptoms in the second month, in both the pregnandiol fell nearly to zero over one or two days at the time of the symptoms. The patient in Case 12 received no progesterone, patient in Case 13 received 5 mg. daily for twelve days. In both of these patients pregnandiol and estrogens rose after the period of symptoms to normal levels, rather more slowly in Case 12. The prolactin in both patients fell to abnormally low values, for one day in Case 12 and for a short period after symptoms had ceased in Case 13. This together with the results in Cases 23, 26 and 29 shows that a temporarily low or even negative value for pregnandiol excretion and a low value for prolactin excretion at this period of pregnancy are not incompatible with continuance of pregnancy to term. In some of the cases no symptoms accompany these low values. They tend to occur at a time when the transfer of function is taking place between the corpus luteum and the placenta, as the site of formation of progesterone. It is, however, difficult to account for the low prolactin values on this basis. In the patient in Case 17 the bleeding which occurred at irregular intervals came in all probability from the eroded cervix. In this patient the assay values were normal in the early part of pregnancy, the estrin was normal late in pregnancy, but the pregnandiol was somewhat low. The patient was slightly toxic later in pregnancy, and this may account for the low pregnandiol values since it has been shown by Weil,<sup>31</sup> Browne, Henry and Venning<sup>11</sup> and Smith and Smith<sup>25</sup> that low values are found in many cases of toxemia in late pregnancy. This case illustrates the necessity for considering the possibility that bleeding during pregnancy is not always threatened abortion and of excluding such cases when considering the effect of therapy on this condition.

The very slight symptoms in the patient in Case 20 perhaps do not justify inclusion as one of threatened abortion. The assays were entirely normal throughout. The patients in the cases in Table III are

the placenta repeatedly fails to take over its function satisfactorily. On the other hand we have seen that other patients who had aborted in one or more previous pregnancies show entirely normal curves of pregnandiol excretion which rise from the level characteristic of the corpus luteum phase of pregnancy at the normal time.

With regard to therapeutic use of progesterone, pregnancy urine extracts, vitamin E, etc., in the treatment of threatened and habitual abortion, numerous claims for good results have been made. The present study shows how difficult it is to evaluate the results of such therapy. The use of gonadotrophic extracts where such large amounts are present as in early pregnancy seems likely to have little effect. In those patients where the prolactin excretion is consistently low, we have seen in most cases the gestation is already degenerate. Good results from the use of progesterone have been reported by Hall,<sup>34</sup> Bishop, Cook and Hampson,<sup>35</sup> Krohn, Falls and Lackner,<sup>36, 37</sup> Kane,<sup>38</sup> Clauberg,<sup>39</sup> Gershenfeld,<sup>40</sup> Elden,<sup>41</sup> and others. In most instances the amounts of progesterone used have been very small: of the order of  $\frac{1}{25}$  of a rabbit unit to 1 rabbit unit per dose with the doses given daily to weekly. This has been due in part to the difficulty in obtaining larger amounts of the material at least until recently, and to its high cost. In those patients with abortion in whom the gestation is degenerate before the onset of symptoms, progesterone is obviously useless given when symptoms appear. A large proportion of these are abnormal from the first, and even if therapy is started before symptoms appear, the result will be unsatisfactory. The patients in whom the embryo and placenta develop up to a certain period, but the placenta takes over the function of progesterone formation late or the corpus luteum degenerates early, offer theoretically the most hopeful outlook for progesterone therapy, since in many, if the critical period can be tided over, the placental function begins and further therapy is unnecessary. It is possible that the determination of prolactin excretion in early pregnancy may enable one to distinguish patients in whom the gestation is already degenerate from those in whom therapy might be of benefit. However, as shown in this investigation, a single determination is of no value, since patients showing temporary low prolactin values in early pregnancy, do carry through to term.

In view of the fact that patients who have aborted once and even those who have aborted more than once (without obvious explanation) and thus fall into the category of habitual abortion may yet in a subsequent pregnancy proceed entirely normally, as far as absence of symptoms and normality of endocrine assays are concerned, it is very difficult to estimate the value of progesterone in this group. Theoretically one should give the progesterone before the time of usual onset of symptoms and continue it over the critical period. The question of dosage is also difficult to determine. From the pregnandiol assays, it seems obvious that the amount of progesterone produced by the corpus luteum up to the seventieth or eightieth day is 5 to 10 mg. per day, and that the placenta produces a gradually increasing amount as pregnancy advances. How much is the minimum requirement is

which a deficiency of corpus luteum hormone is most likely to occur is therefore in the transition period between the ovarian and placental phases (late second and third months); this is the critical period of pregnancy. It has been recognized for a long time that abortion tends to occur most commonly at this period. Henry and others<sup>32</sup> studied the distribution of time of onset of symptoms in 500 cases of abortion (threatened, complete, and incomplete) and found the average day to be the eighty-first from the beginning of the last menstrual period.

As we have seen, some corpora lutea are more readily maintained by pregnancy urine extracts than others, and this may also be true with regard to the maintenance of the corpus luteum by chorionic gonadotrophic substance in early pregnancy. The cause of many abortions as mentioned is a faulty gestation from the first; the chorion partakes in this abnormality and produces an amount of gonadotrophic substance inadequate to prolong the corpus luteum beyond a certain point. In other patients where the gestation is less abnormal, the function of the corpus luteum may be prolonged for the usual time and the embryo develop normally, but the placenta may be slow in taking over. In either case abortion follows. Patients in whom either of these conditions repeatedly occurs habitually abort. We have noted several patients in whom the rise in pregnandiol occurs very late, for example Case 29 (Fig. 8). This patient had had two previous abortions and threatened to abort in the pregnancy under investigation. The pregnandiol did not rise above the level characteristic of the corpus luteum phase until very late. Ordinarily the corpus luteum degenerates at about the third month. It has, however, been shown by Tietze and Wegener<sup>33</sup> that in some cases the corpus luteum may be histologically normal up to term. It seems a possible explanation that on this occasion the patient in Case 29 had such a corpus luteum which produced enough progesterone to carry her until the placenta took over. Incidentally this case shows that the minimum amounts necessary for maintenance of pregnancy are considerably below those usually present. The occasional persistence of a functioning corpus luteum beyond the usual time may explain some of those patients who abort several times and in a subsequent pregnancy carry through to term. It is, of course, equally possible in the patient in Case 29 that the placenta did begin to take over the function of forming progesterone at the usual time and that the low values for pregnandiol, seen about the one hundredth day, occurred at the time of cessation of function of the corpus luteum. The fall in the rate of prolan excretion which occurred at this time would agree better with this explanation on the theory<sup>6</sup> that this fall occurs when the placenta begins to utilize prolan within itself. If the placenta did begin to form progesterone about the one hundredth day in this patient, then the amount which it formed remained low until the one hundred and fiftieth day. The patient in Case 23 who had miscarried on two previous occasions shows this slow rise in pregnandiol, even though there were no abnormal symptoms in the pregnancy investigated. This may indicate that in some cases of repeated abortion



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### DISCUSSION

DR. JEAN PAUL PRATT, DETROIT, MICH.—My assistant, Dr. Stover, has assayed the urine in our abortion cases during the past year. Using the same method as Browne, similar results have been obtained. The method is satisfactory in that it has a sharp end point. Pure crystals of pregnandiol glucuronidate are obtained and the melting point determined.

The average curve of excretion of pregnandiol during menstruation and normal pregnancy is established with reasonable satisfaction. It is noteworthy, however, that a wide variation exists in the individual readings for hormone excretion. The difference amounts to as much as 300 per cent in pregnandiol, 500 per cent in total estrogens, and is even greater in prolan. The same individual varies widely from day to day, and different individuals of course vary. It is evident, therefore, that one cannot wisely interpret single or even a few assays as abnormal. Seven of Browne's patients and four of ours presenting symptoms of abortion, showed low assays of pregnandiol but progressed to full term. Three of his cases and one of ours had no symptoms of abortion but showed low assays of pregnandiol.

I agree with the assumption that there are two sources of progesterin in the human body, the corpus luteum and the placenta. Browne is justified in his interpretation that the rise in pregnandiol excretion, which occurs about the seventieth to ninetieth day in most normal pregnancies, is due to the beginning of secretion by the placenta. I cannot agree with the assumption that if the corpus luteum ceases to produce progesterin for any length of time before the placenta begins to secrete it, abortion will follow.

In one case I reported in 1927 (*Endocrinology* 11: 195, 1927) the corpus luteum of pregnancy was removed on the twentieth day, but the patient continued through a normal pregnancy and delivered an eight-pound baby on the two hundred and seventy-second day after her last menstrual period began. The corpus luteum removed was found to be normal histologically. This patient was deprived of her corpus luteum before chorionic tissue developed to continue the secretion of progesterin. If progesterin is essential to the continuance of pregnancy, there must have been some other source, in this instance, than either the corpus luteum or the placenta.

Several cases are reported in the literature in which the ovaries were removed too early for the chorionic tissue to secrete progesterin. Douglass (*Surg. Gynec. Obst.* 52: 52, 1931) removed the corpus luteum in the fourth week, but the pregnancy continued to term. Corbet (*Irish J. M. Sc.* p. 520, 1932) removed the corpus luteum on the forty-second day without abortion. Unfortunately these patients were observed before pregnandiol excretion was being assayed.

Jones and Weil (*J. A. M. A.* 111: 519, 1938) removed the corpus luteum on the fifty-eighth day. Pregnanndiol decreased to 0 on the sixth postoperative day and reappeared on the fourteenth day. Two explanations may be offered for the

unknown. It is also unknown unless determinations are made how much the patient's own endocrine organs are producing, so that one may be giving 1 mg. of progesterone to a patient in the fourth or fifth month, when she is producing 25 to 50 mg. herself. In any case, it would seem, in view of the above findings, that doses of less than 5 mg. are unlikely to have much effect. This dose should be given daily, or every other day, and may be increased in the presence of persisting symptoms. In most cases either of the threatened or habitual type, therapy should be concentrated during the period of transfer of the function of formation of progesterone from ovary to placenta, since it is at this time that abortion is most likely to occur. If pregnandiol assays are available, a definite rise in pregnandiol excretion may be taken as an index that further therapy is probably unnecessary. The danger of wasting treatment on an already dead fetus, and the uselessness of treating a patient after her own placenta has begun to form normal amounts of progesterone, should always be borne in mind.

#### SUMMARY

1. The physiology of normal pregnancy is discussed from the point of view of the endocrine factors involved.

2. A study has been made of 35 cases of threatened or habitual abortion, and measurement of the excretion of prolactin (chorionic gonadotrophic substance), total estrogens and sodium pregnandiol glucuronide has been made in twenty-four-hour specimens of urine in these patients for varying lengths of time, in some patients throughout pregnancy.

3. A theory of the underlying endocrine basis for abortion is presented.

4. An attempt is made to evaluate progesterone therapy in such cases on a rational basis.

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## A CRITICAL SURVEY OF 1,066 CESAREAN SECTIONS\*

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THE status of cesarean section in obstetric practice is a much debated subject. There are on the one hand those who seek to increase the scope of the operation and, on the other, those who would restrict its use. The ultimate solution of the problem depends upon an unbiased evaluation of the results of operation as opposed to the results of more conservative types of treatment. The error in the final solution will diminish with the increase in statistics considered, and it is with this thought in mind that our paper is presented.

The background of any report is of importance in evaluating results. During the eighteen years covered by this survey the Obstetric Department of the Methodist Hospital of Brooklyn has been composed of men devoting their practice to obstetrics and gynecology. These men have been responsible for the work of both private and ward services and have supervised the small number of patients delivered on the courtesy service. The only change in the staff has been the addition of younger men so that the results shown here present the experiences of a single group of obstetricians under essentially the same leadership. For the past fourteen years the Obstetric Department has been housed in a pavilion separate from the other services. Both private and ward work is included in this report and no cesarean section has been excluded for any reason.

In 1927 one of us (H. S. A.) was assigned the task of collecting cesarean data from the Methodist Hospital for the survey of cesarean section in Brooklyn sponsored by the Brooklyn Gynecological Society and subsequently published. Since that time every cesarean section at the Methodist Hospital has been reviewed by the same individual for presentation at the monthly staff conference. The interest thus aroused and the detail obtained have made possible this presentation.

Table I presents the total figures with the incidence of cesarean section and the gross morbidity and mortality statistics. The incidence of operation is admittedly high, although there is a tendency throughout the country to approach or even exceed our cesarean ratio. The ratio for the private service greatly exceeds that of the ward so far as total figures are concerned; but this discrepancy is lessened when primary cesarean sections alone are considered. This means, of course, that more repeat cesarean sections are performed on the private service. This fact does not, however, reflect a policy of permitting the ward

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behavior of these cases: (1) There may be another source of progestin besides corpus luteum and placenta; or, (2) progestin may not be so important for the continuance of human pregnancy as has been assumed.

DR. C. FREDERIC FLUHMANN, SAN FRANCISCO, CALIF.—The results Browne and his collaborators have obtained in certain cases of habitual abortion are of especial interest and, as more data of this type are accumulated, it will be possible to treat such patients more effectively. It is important to remember, however, that habitual abortion cannot be explained on an endocrine basis in all instances. At other times other factors, not the least of which are the spermatozoa, are primary considerations.

In his graphs I note that the essayist employs the word "prolan" as referring to gonadotrophic substances found in the urine of both nonpregnant and pregnant women. Since these hormones have different biologic properties and probably come from different sources, it seems to me that the word "prolan" should be abandoned owing to the confusion its usage may bring about.

DR. BROWNE (closing).—I would feel that with regard to the removal of the corpus luteum in the cases cited by Pratt before implantation had occurred that there must have been some other source of progesterone. One hesitates to suggest the adrenal cortex as this source, but it is known that progesterone-like activity has been found in this organ.

In regard to the temporary negative values of Jones and Weil, I would emphasize that a negative pregnandiol does not necessarily mean absence of progesterone from the body. There are other links in the chain between progesterone production and excretion of pregnandiol glucuronate. For example, for excretion to occur there must be conjugation of the pregnandiol with glucuronic acid. If there is definite damage to the liver or possibly the kidney, then this will not take place. So that the fact that pregnandiol is temporarily absent after an operative procedure may not mean that progesterone is not present. It may be due to a temporary deviation of glucuronic acid for conjugation with other substances such as is seen after administration of aspirin or to some other interference with the glucuronic acid conjugating mechanism.

Terminology is always a controversial point. I hope that I did not call the gonadotrophic activity present in the normal menstrual cycle "prolan" because one should not say that since it probably differs in its character from the gonadotrophic activity formed in the chorion. The reason that I use the word prolan is that I started doing so when we began our investigations some years ago. I find that to say "chorionic gonadotrophic substance" a hundred times in a lecture takes rather a long time and so I use "prolan" as one would use any abbreviation, and also because it was after all the original term applied to this type of gonadotrophic activity.

With regard to the spelling of the word pregnandiol, I would prefer to leave out the "e" because this was the name originally given to the substance by Butenandt; but while it was correct in German, the chemists tell us that in English the basic hydrocarbon is called "pregnane" and that its di-hydroxy derivative should therefore be called not pregnandiol but pregnanediol.

the mortality rate of the tertiary classical operation and the fourth point of interest is the lack of coordination between maternal morbidity and mortality rates. Where the morbidity rate is low the mortality rate may be high and vice versa. This would indicate that determination of morbidity by temperature readings alone is not completely accurate. Our own standard of morbidity is the usual one of a temperature of 100.4° F. or above on two or more successive days up to the twelfth day but excluding the twenty-four hours immediately post partum.

It has been convenient to subdivide the cases in this series into three periods of six years each. The first period (1920-1925) was before the transfer of the service to its separate pavilion, thus segregating the obstetric department. The second period (1926-1931) was marked by the introduction of the intravaginal use of mercurochrome and the low double flap operation. The last period (1932-1937) witnessed a wider application of the low flap operation and more extensive use of the mercurochrome technique. In Table IV is presented the evolutionary trend over these three periods of the types of operation done. The increase in low classical and low flap operations and the decrease in the high classical operation are in accord with experience throughout the country. Here again in the total figures and in those of the last period there is noted the discrepancy between morbidity and mortality figures. The decidedly lower mortality rate of the low flap operation is clearly shown in the total figures. It is noteworthy that in the last six-year period there was an increase in mortality rate of the classical operation over the previous period, but a decrease in the mortality rate of the low flap operation.

TABLE IV. RELATIONSHIP OF THE THREE SIX-YEAR PERIODS

TYPE OF CESAREAN SECTION	1920-1925	1926-1931	1932-1937	TOTAL
Classical No.	291	297	155	743
Morbidity	132 (45.3%)	112 (37.7%)	95 (61.2%)	339 (45.6%)
Mortality	15 (5.1%)	6 (2.02%)	8 (5.1%)	29 (3.9%)
Low classical No.	1	5	41	47
Morbidity	1 (100%)	3 (60%)	27 (65.8%)	31 (65.9%)
Mortality	0	0	0	0
Low flap No.	1	94	169	264
Morbidity	1 (100%)	34 (36.1%)	121 (71.6%)	156 (59.09%)
Mortality	0	2 (2.1%)	3 (1.7%)	5 (1.9%)

TABLE V. INDICATIONS FOR PRIMARY CESAREAN SECTIONS

INDICATION	TOTAL NO.	1920-1925	1926-1931	1932-1937
Contracted pelvis	401	124	157	120
Pre-eclamptic toxemia and nephritis	74	20	33	21
Uterine inertia and cervical dystocia	67	28	22	17
Placenta previa	35	9	13	13
Previous gynecologic operations	27	10	10	7
Pelvic tumors	23	9	6	8
Cardiac	21	2	8	11
Other medical or surgical complications	15	4	3	8
Malpresentation of fetus	13	0	1	12
Eclampsia	12	4	6	2
Premature separation of placenta	9	5	3	1
Elderly primiparas	6	0	1	5
Congenital malformation of vagina or uterus	5	1	3	1
Pendulous abdomen	2	1	1	0
Miscellaneous	20	3	8	9

patient to deliver vaginally after having undergone abdominal delivery, for in this respect both services are treated identically. A factor in the higher incidence of operation on the private service is the number of cases referred to the obstetrician after a previous unfortunate experience. In support of this may be cited the fact that of 401 primary cesarean sections done for bony dystocia, 106 had suffered the loss of at least one normal baby from attempted vaginal delivery.

The gross maternal morbidity rate is just over 50 per cent and the mortality rate is 3.18 per cent. These figures are not unlike those of similar clinics, being neither the lowest reported nor by any means the highest. The total fetal mortality rate of 5.2 per cent, which includes all stillbirths and neonatal deaths from all causes, indicates that cesarean section is no certain guaranty of the survival of the infant.

In Table II the cesarean sections are divided into primary and repeat operations. The ratio of primary to repeat cases is more than two to one. The close similarity of the morbidity and mortality rates is interesting.

In Table III the various types of operations comprising the primary and repeat groups are further analyzed. Several points should be noted in this analysis. The first is the lower maternal mortality rate in the primary low flap operations as compared with the classicals. The second is the absence of maternal mortality in the secondary low flap operations, while the secondary classical operations show approximately the same rate as the primary ones. A third is the increase in

TABLE I. GENERAL DATA

Total deliveries Jan. 1, 1920, to Jan. 1, 1938	27,234
Total cesarean sections Jan. 1, 1920, to Jan. 1, 1938	1,066
Total cesarean ratio	1 in 25.5 (3.9%)
Private cesarean ratio	1 in 18.09 (5.5%)
Ward cesarean ratio	1 in 60.0 (1.6%)
Primary cesarean ratio	1 in 37.2 (2.6%)
Private primary cesarean ratio	1 in 29.04 (3.4%)
Ward primary cesarean ratio	1 in 78.06 (1.04%)
Total morbidity	534 (50.09%)
Total maternal mortality	34 (3.18%)
Total fetal mortality	56 (5.2%)

TABLE II. PRIMARY AND REPEAT CESAREAN SECTION

	NUMBER	MORBIDITY	MORTALITY
Primary cesarean sections	730	377 (51.6%)	23 (3.1%)
Repeat cesarean sections	331	152 (45.9%)	11 (3.3%)
Not classified	5	5	0

TABLE III. TYPES OF OPERATION PERFORMED

TYPE OF OPERATION	NUMBER	MORBIDITY	MORTALITY
Primary classical	484	236 (48.7%)	18 (3.7%)
Primary low classical	28	20 (71.4%)	0
Primary low flap	206	112 (54.2%)	5 (2.4%)
Porro	10	7 (70%)	0
Latzko	1	1 (100%)	0
Vaginal cesarean section	1	1 (100%)	0
Secondary classical	206	75 (36.4%)	8 (3.8%)
Secondary low classical	19	11 (57.8%)	0
Secondary low flap	54	39 (72.2%)	0
Tertiary classical	44	22 (50%)	2 (4.5%)
Tertiary low flap	4	4 (100%)	0
Quartan classical	3	0	0

any conditions, and despite the fact that the cases here presented were those exhibiting the most severe signs and symptoms, the high mortality rate of cesarean section in the toxemias of pregnancy requires serious consideration.

Eclampsia presents a problem even more important than the one just considered. Table VIII presents our experiences with this complication. As was shown in Table VI, we have markedly reduced the number of patients operated upon because of eclampsia. The maternal mortality is too high and all the mortality in our eclamptic patients was referable to the cardiovascular system.

Primary cesarean section because of uterine inertia and cervical dystocia shows a higher maternal mortality rate (Table IX) and higher maternal morbidity rate than the series as a whole. These patients were necessarily subjected to the longest labors and were more frequently subjected to ruptured membranes than any other group. The causes of mortality are of interest. One death was from sepsis. The other two deaths were from pulmonary embolus, the only fatalities following primary cesarean section from this cause. The results of the low flap operation were appreciably better in this group than were those of the high classical operation.

Cesarean section, in the last few years, has come to play a more important role in the management of placenta previa. Those patients who were operated upon primarily for placenta previa (Table X) showed a morbidity higher than average but no maternal mortality. Two factors have contributed largely to this lack of maternal mortality; first, elective operation—none of these patients had ruptured membranes or were subjected to any labor; second, the free use of transfusions. All these patients are typed on admission and there is no hesitation in giving frequent large transfusions, before, during, or after operation.

The mortality rate in patients who were subjected to cesarean section because of previous gynecologic operations (Table XI) is very high, comparable to the

TABLE VIII. PRIMARY CESAREAN SECTIONS FOR ECLAMPSIA

	NUMBER	MORBIDITY	MORTALITY
Total	12	9 (75%)	2 (16.6%)
Classical cesarean sections	9	8 (88.8%)	2 (22.2%)
Low classical cesarean sections	1	1 (100%)	0
Low flap cesarean sections	2	0	0
Classical deaths: Cardiac 1; cerebral embolus 1			
Secondary cesarean sections where eclampsia was a definite factor			
Classical cesarean sections	1	1	1
Classical death—cardiac			

TABLE IX. PRIMARY CESAREAN SECTIONS FOR UTERINE INERTIA AND CERVICAL DYSTOCIA

	NUMBER	MORBIDITY	MORTALITY
Total	67	39 (57.9%)	3 (4.4%)
Classical cesarean sections	37	20 (54%)	2 (5.4%)
Low classical cesarean sections	2	2 (100%)	0
Low flap cesarean sections	28	17 (60.7%)	1 (3.5%)
Classical deaths: Sepsis 1; pulmonary embolus 1			
Low flap death: Pulmonary embolus 1			

TABLE X. PRIMARY CESAREAN SECTIONS DONE FOR PLACENTA PREVIA

	NUMBER	MORBIDITY	MORTALITY
Total	35	21 (60%)	0
Classical cesarean sections	33	19 (57.5%)	0
Low classical cesarean sections	1	1 (100%)	0
Low flap cesarean sections	1	1 (100%)	0

The most important aspect of the primary cesarean section is the indication therefor. This is of particular interest because this indication not only subjects the patient to the first operation, but in most instances determines the procedure in subsequent pregnancies. Table V lists the various indications for primary cesarean sections and subdivides the cases into the three six-year periods, thus giving opportunity for comparison regarding the continued application of any indication. Contracted pelvis accounts for about 55 per cent of the cases, and this proportion is maintained throughout the three periods. In most surveys pre-eclampsia and nephritis occupy the second place in listing indications. Our series is no exception. Here again the proportion remains about the same over the three periods. Uterine inertia and cervical dystocia, previous gynecologic operations, eclampsia, and accidental hemorrhage have decreased over the years in frequency as indications for cesarean section. However, such indications as placenta previa, cardiac, other medical and surgical complications, malpresentations of the fetus, and elderly primiparas have supplanted them. The increase in operations done for certain malpresentations is particularly striking and is due to earlier recognition of the condition, frequently by means of x-ray, at a time when operation is safer.

Further inquiry into the results of cesarean section done for a specific indication or accompanied by complications reveals certain facts. Table VI is an analysis of the primary cesarean sections operated because of contracted pelvis. The classical operation would seem at first glance to offer greater safety. The causes of death, however, give rise to some concern about this operation. Three of the four deaths following the classical operation were from sepsis. None of the deaths following the low flap operation were from this cause. When we consider that the low flap operation was done after an average of six hours' longer labor and more frequently after rupture of the membranes, it will be seen that this operation was subjected to a severer test than was the classical. Another point of considerable interest is the definitely lower mortality for this group than for the series as a whole.

Table VII presents not only the patients operated primarily for pre-eclampsia and nephritis but also those in whom these complications were a definite factor, despite the listing of another condition as the most potent indication. In these cases the maternal mortality was over twice that of the series as a whole. And while patients exhibiting severe tonic symptoms do show a higher mortality under

TABLE VI. PRIMARY CESAREAN SECTIONS FOR CONTRACTED PELVIS

	NUMBER	MORBIDITY	MORTALITY
Total	401	203 (50.6%)	8 (1.99%)
Classical cesarean sections	253	117 (46%)	4 (1.5%)
Low classical cesarean sections	10	7 (70%)	0
Low flap cesarean sections	138	79 (57.2%)	4 (2.9%)
Classical deaths: Sepsis 3; pneumonia 1			
Low flap deaths: Cardiac 1; pneumonia 1; intestinal obstruction 1; paralytic ileus 1			

TABLE VII. PRIMARY CESAREAN SECTIONS FOR PRE-ECLAMPTIC TOXEMIA AND NEPHRITIS

	NUMBER	MORBIDITY	MORTALITY
Total	74	36 (48.6%)	5 (6.7%)
Classical cesarean sections	58	24 (41.3%)	5 (8.6%)
Low classical cesarean sections	7	5 (71.4%)	0
Low flap cesarean sections	9	7 (77.7%)	0
Classical deaths: Sepsis 2; hemorrhage 1; acute hepatitis 1; cardiac 1			
Other cesarean sections where toxemia was a definite factor			
Classical cesarean sections	19	11	1
Classical death—volvulus			



tions, for individual circumstances require the closest scrutiny and cooperation with the medical or surgical consultant.

The group of patients operated upon because of malpresentation of the fetus (Table XV) is small. The cause of death in the one fatal case occurring in this group bears no relation to the indication for operation, but does reflect upon the type of operation done and the length of time consumed in its performance. Most of these patients were operated upon either electively or after a very short test of labor. The one death occurred after an elective operation. Individual factors and supplementary indications, such as slight pelvic contraction, parity, and size of the baby, must play a considerable part in the determination to subject the patient to cesarean section for fetal malpresentation. Another instance of the necessity for individualization.

Premature separation of the placenta (Table XVI) as an indication for cesarean section has not exhibited the excellent fetal results that might be expected, 7 of the babies having died at or shortly after birth. The maternal results, in the small number of cases presented, were excellent, but these same maternal results can be obtained by vaginal delivery. It will be recalled from Table V that this indication has shown a decrease in frequency over the years.

Those elderly primiparas (Table XVII) who were subjected to cesarean section because of their age showed excellent results. These cases were elective and in all the membranes were intact.

The few cesarean sections performed (Table XVIII) for congenital malformation of vagina or uterus are comparable to those done for age of the primipara. These were elective operations and the results were entirely satisfactory.

The results of the repeat cesarean sections (Table XIX) show a higher mortality but a lower morbidity than the series as a whole. All of the deaths in this group followed repetition of the high classical operation. Consideration of the

TABLE XV. PRIMARY CESAREAN SECTIONS FOR MALPRESENTATION OF FETUS

	NUMBER	MORBIDITY	MORTALITY
Total	13	12 (92.3%)	1 (7.6%)
Classical cesarean sections	5	5 (100%)	1 (20%)
Low classical cesarean sections	0	0	0
Low flap cesarean sections	8	7 (87.5%)	0
Classical death: Intestinal obstruction			

TABLE XVI. PRIMARY CESAREAN SECTIONS FOR PREMATURE SEPARATION OF THE PLACENTA

	NUMBER	MORBIDITY	MORTALITY
Total	9	4 (44.4%)	0
Classical cesarean sections	8	3 (37.5%)	0
Low classical cesarean sections	1	1 (100%)	0
Low flap cesarean sections	0	0	0
Others where accidental hemorrhage was found			
Classical cesarean sections	5	2	1
Classical death: Hemorrhage			

TABLE XVII. PRIMARY CESAREAN SECTIONS FOR "ELDERLY PRIMIPARAS" (35 YR. OR OVER)

	NUMBER	MORBIDITY	MORTALITY
Total	6	1 (16.6%)	0
Classical cesarean sections	0	0	0
Low classical cesarean sections	1	0	0
Low flap cesarean sections	5	1 (20%)	0

TABLE XI. PRIMARY CESAREAN SECTIONS DONE FOR PREVIOUS GYNECOLOGIC OPERATIONS

	NUMBER	MORBIDITY	MORTALITY
Total	27	13 (48.1%)	2 (7.4%)
Classical cesarean sections	19	9 (47.3%)	2 (10.5%)
Low classical cesarean sections	2	1 (50%)	0
Low flap cesarean sections	6	3 (50%)	0
Classical deaths: Sepsis 2			

rate in the toxemia group. Many of these patients were subjected to labor before cesarean section was deemed necessary. The high mortality suggests either that sterilization should have been done at the time of the gynecologic operation or that cesarean section should have been performed earlier in labor. The two fatal cases had been subjected to prolonged labor. The operative time was not prolonged in either instance. Both deaths were due to sepsis.

The primary cesarean sections performed because of pelvic tumors showed no maternal mortality (Table XII). None of these patients was subjected to more than a very short labor and the majority were done as elective operations. This group was comparable to the placenta previa group in its satisfactory result.

Those patients (Table XIII) who had cesarean section primarily for cardiac disease showed a slightly higher morbidity and mortality rate than the average of the series as a whole. When it is considered that these patients represented the least favorable cases, the mortality rate, one death from cardiac failure, is most encouraging. The number of patients operated upon for this condition shows an increase and the results justify a continuation of the use of cesarean section in properly selected cases.

As regards the other medical and surgical complications, diabetes, acute appendicitis at or near term, intra-partum intestinal obstruction, etc. (Table XIV), the mortality rate in this small series of 15 cases has been excellent. This should not, however, encourage too widespread use of cesarean section for these indica-

TABLE XII. PRIMARY CESAREAN SECTIONS DONE FOR PELVIC TUMORS

	NUMBER	MORBIDITY	MORTALITY
Total	23	12 (52.1%)	0
Classical cesarean sections	18	10 (55.5%)	0
Low classical cesarean sections	1	0	0
Low flap cesarean sections	4	2 (50%)	0

TABLE XIII. PRIMARY CESAREAN SECTIONS DONE FOR CARDIAC DISEASE

	NUMBER	MORBIDITY	MORTALITY
Total	21	11 (52.3%)	1 (4.7%)
Classical cesarean sections	18	10 (55.5%)	1 (5.5%)
Low classical cesarean sections	2	1 (50%)	0
Low flap cesarean sections	1	0	0
Classical death: Cardiac 1			

TABLE XIV. PRIMARY CESAREAN SECTIONS DONE FOR OTHER MEDICAL OR SURGICAL COMPLICATIONS

	NUMBER	MORBIDITY	MORTALITY
Total	15	9 (60%)	0
Classical cesarean sections	13	7 (53.8%)	0
Low classical cesarean sections	0	0	0
Low flap cesarean sections	2	2 (100%)	0

deaths in those operated upon by the classical technique; it does not appear as a cause of death after the low flap technique. Of the fatal cases in the classical group 2 had ruptured membranes, 4 unruptured; in the low flap group 1 had ruptured membranes, 4 unruptured. A definite factor in the low flap group is the length of operating time. Three of these 5 cases were subjected to unusually long operations; in each instance the patient was quite obese and the low flap technique was more time consuming. In other words, the deaths in the low flap group, after more than twelve hours of labor, might be more properly assigned to the operator and those of the classical group to the operation.

In Table XXI is presented the relationship of the condition of the membranes to maternal mortality and morbidity. In this connection both primary and repeat cesarean sections are considered. There are included for study here only those cases in which the condition of the membranes was definitely stated. A point of considerable interest is the fact that those patients having ruptured membranes exhibited a lower total maternal mortality than those with membranes intact. The list of causes of death, however, brings out the true status here. It will be noted that of the 586 patients with intact membranes there were 4 deaths from sepsis. Of the 265 patients with ruptured membranes, there were 5 deaths from sepsis. This means that with ruptured membranes the mortality from sepsis is more than twice as great. It must be remembered that the patients with unruptured membranes include many patients whose general condition was disturbed by such conditions as toxemia of pregnancy, heart disease, etc., while those patients with ruptured membranes, particularly those with membranes ruptured

TABLE XX. MATERNAL MORBIDITY AND MORTALITY IN RELATION TO LABOR

	NUMBER	MORBIDITY	MORTALITY
Primary classical (no labor)	208	99 (47.6%)	8 (3.8%) <sup>1</sup>
Primary low flap (no labor)	50	24 (48%)	0
Primary classical (under 12 hr.)	142	63 (44.3%)	4 (2.1%) <sup>2</sup>
Primary low flap (under 12 hr.)	43	22 (51.1%)	0
Primary classical (over 12 hr., av. 25.9 hr.)	134	74 (55.2%)	6 (4.4%) <sup>3</sup>
Primary low flap (over 12 hr., av. 31.1 hr.)	113	66 (58.3%)	5 (4.4%) <sup>4</sup>

<sup>1</sup>Causes of death: Sepsis 2, cardiac 2, hemorrhage 1, cerebral embolus 1, acute hepatitis 1, intestinal 1.

<sup>2</sup>Causes of death: Sepsis 3, pneumonia 1.

<sup>3</sup>Causes of death: Sepsis 4, cardiac 1, pulmonary embolus 1.

<sup>4</sup>Causes of death: Intestinal 2, pneumonia 1, cardiac dilatation 1, pulmonary embolus 1.

TABLE XXI. CONDITION OF MEMBRANES IN RELATION TO MORBIDITY AND MORTALITY

	NUMBER	MORBIDITY	MORTALITY
Membranes intact	586	272 (46.4%)	21 (3.5%) <sup>1</sup>
Membranes ruptured	265	151 (56.9%)	9 (3.4%) <sup>2</sup>
Time undetermined	37	25	2 <sup>3</sup>
Up to 12 hours	138	73 (52.9%)	4 (2.9%) <sup>4</sup>
12 to 24 hours	49	25 (51.0%)	2 (4.08%) <sup>5</sup>
Over 24 hours	41	28 (68.2%)	1 (2.4%) <sup>6</sup>

<sup>1</sup>Causes of death: Intestinal 8, sepsis 4, pulmonary embolus 2, hemorrhage 2, cardiac 2, pneumonia 1, acute hepatitis 1, cerebral embolus 1.

<sup>2</sup>Causes of death: Sepsis 5, cardiac 2, pneumonia 1, pulmonary embolus 1.

<sup>3</sup>Causes of death: Sepsis 2.

<sup>4</sup>Causes of death: Sepsis 1, cardiac 1, pneumonia 1, pulmonary embolus 1.

<sup>5</sup>Causes of death: Sepsis 2.

<sup>6</sup>Cause of death: Cardiac 1.

TABLE XVIII. PRIMARY CESAREAN SECTIONS FOR CONGENITAL MALFORMATIONS OF VAGINA OR UTERUS

	NUMBER	MORBIDITY	MORTALITY
Total	5	3 (60%)	0
Classical cesarean sections	3	2 (66.6%)	0
Low classical cesarean sections	0	0	0
Low flap cesarean sections	2	1 (50%)	0

TABLE XIX. REPEAT CESAREAN SECTIONS

	NUMBER	MORBIDITY	MORTALITY
Total	331	152 (45.9%)	11 (3.3%)
Classical cesarean sections	254	98 (34.3%)	11 (4.3%)
Low classical cesarean sections	19	11 (57.8%)	0
Low flap cesarean sections	58	43 (74.1%)	0
All classical: Cardiac 2, pulmonary embolus 2, hemorrhage 1, sepsis 1, intestinal paresis 2, intestinal obstruction 3			

causes of death is of considerable interest. Five of the 11 deaths were attributed to intestinal obstruction, the result of either paresis or adhesions. This high frequency of fatal intestinal complications is in line with our impression of a higher incidence of serious intra-abdominal adhesions following the high classical technique. The low flap operation, as is well known, is not so frequently followed by these complications. While the number of repeat low flap operations is not comparable to that of the high classicals the difference in mortality rates is so striking as to cause comment. The lower incidence of adhesions following the low flap technique is a factor in this difference. Two deaths in this group occurred in patients who suffered a rupture of the previous scar. Since there is less danger of rupture of the low flap scar these two deaths might have been avoided had the previous operation been by the low flap rather than the high classical technique. Pulmonary embolus was the actual cause of death in these two cases. The results of the repeat cesarean sections furnish considerable evidence of the superiority of the low flap technique.

It should be noted in considering the causes of death listed here that sepsis appears as the cause of death in only one repeat cesarean section. In contrast to this may be cited the fact that in 484 primary high classical operations fatal sepsis occurred eight times. This may, at least in part, be accounted for by the fact that elective operations were routinely performed in the repeat group.

A study of the relationship of labor to maternal morbidity and mortality affects chiefly the primary cesarean sections, for it is our routine practice to deliver by prompt elective cesarean section, any patient who has been previously subjected to this operation. Table XX is a comparative study of the results of labor with reference to the high classical and low flap techniques. Unless causes of death are considered in this connection the bare figures are difficult to interpret. The higher mortality in the elective group of classical cases as compared with those subjected to labor of one to twelve hours' duration must be supplemented by this list of causes of death. It will be noted that sepsis occurs twice in the eight deaths of the elective group and three times in the four cases of the group subjected to moderate labor. Further, it will be noted that several of the deaths in the elective group relate to the indication for operation rather than to the operation itself, i.e., the cardiac death was in a patient operated upon because of cardiac disease, the acute hepatitis and cerebral embolus in patients operated upon because of toxemia of pregnancy. It is also interesting that of the fatal cases in the elective group only one patient had ruptured membranes; this was one of the deaths from sepsis. In the group subjected to moderate labor, 3 of the 4 patients had ruptured membranes.

Of the two groups subjected to labor of over twelve hours' duration, the mortality rates are identical. Sepsis, however, appears as the cause of four

Our experience with both local anesthesia and avertin has been very limited and the small number of cases does not permit intelligent comment. Local anesthesia is coming to assume more importance, and its use is being successfully extended in our clinic. Three of the four deaths listed here under local anesthesia were due to intestinal obstruction following repeat classical operations. The fourth death was from pneumonia, local anesthesia having been used because of severe upper respiratory infection.

Table XXIV presents the causes of morbidity according to the type of cesarean section performed. The unexplained morbidities include those where "reaction" was given as the cause. All these morbidities were of short duration, two to three days, and did not cause any prolongation of hospital stay. The group that would be considered as sepsis, i.e., pelvic thrombophlebitis, pelvic peritonitis, bacteriemia, peritonitis and puerperal sepsis, was much more prevalent after classical than after low flap operations. The milder grades of infection, including sapremic infections, were more nearly equally divided between the two types of operations, since the ratio of classical to low flap operations was approximately three to one. This relationship also holds for the number of infected wounds. There were two instances, both following low flap operations, in which there was complete rupture of the wound. Both these occurred in patients who had severe pulmonary infections, pneumonia and bronchitis, but both survived.

TABLE XXIV. CAUSES OF MORBIDITY

	CLASSICAL	LOW CLASSICAL	LOW FLAP
Unexplained (includes "reaction" temperatures)	180	17	104
Infected wound	42	3	12
Peritonitis	4	0	0
Pelvic infection	6	1	2
Puerperal sepsis	4	0	0
Pelvic thrombophlebitis	2	0	0
Bacteriemia	2	0	0
Respiratory infections	23	2	11
Sapremia (lochia metra)	33	4	12
Pyelitis	12	1	9
Phlebitis	12	1	3
Hemorrhage	5	0	0
Breast infections	3	1	0
Eclampsia	3	0	0
Paralytic ileus	2	0	2
Parotitis	2	0	1
Axillary abscess	2	0	0
Abscess of uterine wall	2	0	0
Acute colitis	0	1	0
Acute cholecystitis	0	0	1

Post-partum hemorrhage was considered the cause of morbidity in 5 cases. This complication occurred in a total of 9 cases in the series and in 2 instances was the cause of death. The majority of these cases occurred after the high classical operation and both fatal cases were included in these. One hemorrhage followed the successful use of local anesthesia, 1 followed spinal and 7 followed general anesthesia.

One other complication, while not listed as a cause of morbidity, deserves mention. There were 8 patients in whom rupture of the previous cesarean scar occurred. Four of these patients had had 2 previous high classical cesarean sections, 3 had had 1 previous high classical operation, and 1 patient had had a previous low flap operation. Two deaths occurred in the 8 cases, both in patients who had had two previous high classical operations. The cause of death in each instance was pulmonary embolus. In 3 instances the rupture caused no symptoms and was found at routine repeat operation before the onset of labor.

over twelve hours, include the patients in good general condition; the indication for whose operation was contracted pelvis. And it must be remembered that the patients operated upon because of contracted pelvis exhibited the lowest maternal mortality. The fact that no sepsis deaths occurred in the group with membranes ruptured over twenty-four hours may be explained by the greater use of the low flap technique in these cases.

A comparative study of the effects of ruptured membranes on the outcome after use of the high classical and low flap techniques is made in Table XXII. The mortality rate for the low flap is higher in those patients with membranes intact, but the low flap mortality includes no case of sepsis; the classical list includes four such deaths. Where there has been rupture of the membranes, one-half of the deaths after classical cesarean section are from sepsis, and the mortality rate from the classical operation far exceeds that of the low flap. The classical cesarean section is much more likely to be followed by fatal sepsis when the barrier of intact membranes has been removed.

Anesthesia (Table XXIII) is of importance in considering cesarean sections. General anesthesia, consisting of gas, oxygen, and ether, was by far the most frequently used. Twenty-one respiratory infections followed the use of general anesthesia. Included in these was one fatal case of pneumonia. In our clinic the results from general anesthesia have been very satisfactory because of its administration by a staff of properly trained nurses.

Spinal anesthesia was used in 90 cases with no maternal mortality and with a lower morbidity than the average of the series. Twenty-six of these cases were toxic patients and the results in them were excellent. Three respiratory infections were encountered following this type of anesthesia. These patients had respiratory infections before operation. Spinal anesthesia has not been established as a routine in our service but has been used only on indication. Upper respiratory infections and toxemia are the most frequent such indications. When properly indicated and when given by those experienced in its use spinal anesthesia has a definite place in cesarean section and many clinics would do well to use it more frequently.

TABLE XXII. COMPARISON OF LOW FLAP AND CLASSICAL AS TO CONDITION OF MEMBRANES

	NUMBER	MORBIDITY	MORTALITY
Membranes intact			
Classical	469	194 (41.3%)	17 (3.6%) <sup>1</sup>
Low flap	84	54 (64.2%)	4 (4.7%) <sup>2</sup>
Membranes ruptured up to 12 hr.			
Classical	92	44 (47.8%)	4 (4.3%) <sup>3</sup>
Low flap	39	25 (64.1%)	0
Membranes ruptured over 12 hr.			
Classical	42	25 (59.5%)	2 (4.7%) <sup>4</sup>
Low flap	47	27 (57.4%)	1 (2.1%) <sup>5</sup>

<sup>1</sup>Causes of death: Intestinal 6, sepsis 4, pulmonary embolus 1, hemorrhage 2, cardiac 2, acute hepatitis 1, cerebral embolus 1.

<sup>2</sup>Causes of death: Intestinal 2, pneumonia 1, pulmonary embolus 1.

<sup>3</sup>Causes of death: Sepsis 1, cardiac 1, pneumonia 1, pulmonary embolus 1.

<sup>4</sup>Causes of death: Sepsis 2.

<sup>5</sup>Cause of death: Cardiac 1.

TABLE XXIII. ANESTHESIA

TYPE	NUMBER	MORBIDITY	MORTALITY
Avertin	5	4 (80.0%)	0
Local	38	22 (57.8%)	4 (10.5%)
Spinal	90	44 (48.8%)	0
General	933	464 (49.7%)	30 (3.2%)

which demands and provides for careful supervision of younger men by those of greater experience. This factor of personal experience must receive due consideration in evaluating any group of figures.

In concluding this survey, stress must be laid upon certain points. The maternal mortality of cesarean section is high, too high following some indications, particularly the toxemias of pregnancy. These weak spots must either be eradicated or bolstered by a change in technique. Because of its greater incidence of sepsis and poorer results in repeat operations, the classical operation should be reserved for those cases where the element of time is of prime importance. The low flap operation is slightly more difficult in its performance, particularly in the obese patient, and the mortality associated with it can be more frequently attributed to the operator than to the operation. If cesarean section is to take its proper place as a means of escaping obstetric difficulties, the following postulates must be rigidly observed: There must be a correct indication for operation. The proper type of operation must be performed at the proper time. The operation must be performed by an obstetrician with surgical experience.

643 ST. MARKS AVENUE

632 SECOND STREET

In Table XXV is a recapitulation of the most important consideration in cesarean section, maternal deaths. There were 34 fatalities in our series, and the various causes are listed. The high classical technique is credited with 29 of these deaths, the low flap with 5. We have discussed most of these cases from the point of view of indication for operation, but certain factors should be stressed. No deaths from sepsis occurred following the low flap technique. The greatest number of deaths from intestinal complications occurred after repetition of the high classical technique. The cardiovascular deaths occurred, in one patient operated upon because of cardiac disease, and in 4 patients operated upon because of toxemia or eclampsia; in the other 2 cases death was attributed to acute cardiac dilatation although shock may have been the underlying cause. The deaths from pulmonary embolus were equally divided between the patients with rupture of the previous scar and those patients operated upon because of uterine inertia and cervical dystocia. Only 2 patients died of pneumonia and 2 of hemorrhage. One patient died of acute fulminating hepatitis. Our present knowledge presents no solution to this problem.

TABLE XXV. MATERNAL DEATHS

	CLASSICAL		LOW FLAP		TOTAL
	PRIMARY	REPEAT	PRIMARY	REPEAT	
Sepsis	8	1	0	0	9
Intestinal obstruction (Including paresis)	2	5	2	0	9
Cardiovascular	4	2	1	0	7
Pulmonary embolus	1	2	1	0	4
Pneumonia	1	0	1	0	2
Hemorrhage	1	1	0	0	2
Acute hepatitis	1	0	0	0	1
No deaths followed low classical operations					

## SUMMARY

In the face of bare figures, the high classical technique stands convicted of a high maternal mortality, 3.9 per cent for all the classical operations as against 1.8 per cent for all the low flap operations. It has been shown, however, in this analysis that type of operation alone cannot be condemned. The classical technique bore the brunt of responsibility for such indications as toxemia and nephritis and cardiac and pulmonary diseases where the patient did not enter the operating room in good general physical condition, and where speed of operation was a most important consideration. There was one instance, however, where the high classical operation did fail badly, namely in the prevention of sepsis. The low flap technique has in this series been responsible for no fatality from sepsis. As was shown in the discussion on labor the fatal cases following the low flap technique were attributable more to the technique of the operator than to the technique of the operation. The factor of experience of the obstetrician is one that cannot be overlooked. In listing the fatal cases in chronologic order and including the name of the operator, in preparing this study, it was an outstanding fact that the younger men of the service were much more frequently associated with maternal mortality. As time progressed and these men became more experienced their names did not nearly so frequently appear in this listing. This fact is noteworthy, for it occurred in spite of the organization of our service



The same classification of operations is used in this report. Nevertheless the radical procedure (supravaginal hysterectomy) was not performed because of infection, but for the purpose of sterilization or removal of a myomatous uterus.

Harris and J. H. Brown<sup>1</sup> found positive uterine cultures in 44 per cent of their series of 50 cases. They noted the predominance of anaerobic streptococci. Anaerobic growth was obtained in 45 per cent of the positive cultures. "No sterile cultures were obtained from patients in whom active labor had lasted for six hours or more and only one positive culture was obtained where labor had progressed less than six hours." "... when cesarean section is definitely indicated the ideal time for its performance is at an appointed time at the end of pregnancy or at the very beginning of labor." Later in labor they suggest employment of the low cervical section or the radical procedure (supravaginal hysterectomy). Antiseptic treatment of the vagina preparatory to operation was not mentioned in their paper.

Douglas and Rhees<sup>6</sup> studied cultures of the uterus in a series of 20 cesarean sections and obtained positive cultures on 7, or 30 per cent. Six of these patients had been in labor for an average of 27.9 hours. Anaerobic streptococci were most frequently found. No vaginal preparation was mentioned in this group of cases. "All patients on whom cesarean section was performed and who showed positive uterine cultures at the time of operation, later developed febrile puerperia."

Dieckmann<sup>7</sup> stressed the importance of infection as the main cause of mortality in 945 cesarean sections, 50 per cent.

#### DISCUSSION

The use of vaginal instillations during labor was instituted on our service by Dr. W. J. Dieckmann (1926). At first they consisted of a 3 per cent mercurochrome and 0.03 per cent iodine solution in glycerin. This resulted in a definite improvement in morbidity and mortality. On Jan. 1, 1931, at the suggestion of Dr. E. A. Graham, the type of instillation used was changed to 1 per cent neutral acriflavine in glycerin. This was done because of the rather specific affinity of acriflavine for cocci. The chief offenders in our study had been shown to be anaerobic streptococci. Eight cubic centimeters of the solution were instilled into the vagina upon admission of the patient and before subsequent examinations. Later this treatment of the vagina was carried out every six hours during labor, and for several years has been ordered every four hours. In numerous cases the degree of penetration of this dye substance has been observed to extend four inches above the external os.

To prepare the vagina before a gynecologic procedure and not to do so before cesarean section, appears somewhat inconsistent. In the latter case the peritoneal cavity is exposed to contamination from the vagina, and in the former there may be no such exposure. The type of positive cultures obtained from the uteri at section is similar to those of the vaginal flora, 83 per cent anaerobic. Soule and the author studied the vaginal flora of normal clinic patients during pregnancy and found anaerobic growth in 60 per cent of the cases. The vagina seems to be the most logical source of contamination in cesarean section, and the use of

## BACTERIOLOGY OF THE UTERUS AT CESAREAN SECTION\*

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**A**N ANALYSIS of 144 uterine cultures taken at cesarean section is presented in order to demonstrate the apparent value of antiseptic vaginal instillations in the preparation of the patient for operation. Cultures were obtained from 52 per cent of the patients operated upon during a period of eight years at the St. Louis Maternity Hospital. The causes of mortality were determined and the elimination of infection as an important factor will be noted. A very practical finding is that when a case has received the benefit of antiseptic vaginal instillations before operation the time of operation may be safely postponed much longer than has been formerly recommended.

The report of Harris and J. H. Brown,<sup>1</sup> in 1927, suggested the idea and method of culturing the uterus at cesarean section. They stated "the excessive maternal mortality is due in great part at least, to the fact that it is not generally recognized that the danger of the operation increases progressively with every hour elapsing after the onset of labor, and is explained by finding that an ascending infection of the uterus occurs whenever labor has progressed for some time. Williams,<sup>2</sup> in 1917, first adduced histologic evidence concerning the occurrence of such infections, which was still further confirmed when one of us (J. W. H.<sup>3</sup>) demonstrated its existence in 22 of 33 uteri removed by supravaginal hysterectomy following cesarean section when labor had lasted six or more hours.

"Walthard,<sup>4</sup> in 1919, reported that positive cultures were obtained from the amniotic fluid and uterine secretion at 15 cesarean sections. He failed to state how long the patients had been in labor when the operation was done, but most of them had been in the hands of midwives or physicians before admission to the clinic, and in all of them five to eighty hours had elapsed between the rupture of the membranes and the time of operation."

The same method of obtaining the culture was used in the present study as described by Harris and J. H. Brown.<sup>1</sup> "All of the cultures were taken through the uterine incision, in order to insure that they could not be contaminated by the vaginal secretion. As soon as the child was delivered, and before the hands or the instruments had been introduced into the lower uterine segment, a sterile, cotton-covered swab was passed through the uterine incision and rubbed over the lower uterine segment, care being taken that it did not come in contact with any portion of the uterus except that from which the culture was desired." The cultures should be inoculated as soon as possible and smears made and stained with Gram's stain. Three tube cultures are made routinely: an aerobic blood agar slant, a cooked meat tube, and an anaerobic blood agar slant using Wright's<sup>5</sup> technique. This method has been found to be practical and satisfactory in the search for anaerobic organisms.

\*Read, by invitation, at the Sixty-fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

TABLE III. ST. LOUIS MATERNITY HOSPITAL. CESAREAN SECTIONS, CLASSICAL

Total cases by this method				47
POSITIVE CULTURES				NEGATIVE CULTURES
Receiving acriflavine in glycerin	Aerob.	Mixed—1	Anaerob.	41
(Intra partum)				
Not receiving acriflavine in glycerin	Aerob.	Mixed	Anaerob.—1	4
Elective				42
Afebrile				33
Ruptured membranes				11
Extremes—40 minutes to 56½ hours				
In labor				9
Extremes—2 hours to 74 hours (3 less than 6 hours, 6 more than 6 hours)				
Vaginal examination				15
Excellent healing of wound				41
DeLee shuttle				15
Deaths				0
Temperature: 37.5° C. or more on day of operation				1
Considered afebrile if cause of fever was outside genital tract.				

Table III analyzes the group of classical sections of Table II in more detail. One case with a positive culture was found to be a mixed contamination, with both aerobic and aerobic organisms. Instillations were not started until late in labor because the patient was not admitted to the hospital until intra-partum infection was present. Another patient showed anaerobic growth and had received no instillations. It was an elective section and the membranes were intact. This seems to lend further support to the idea that intact membranes are permeable to bacteria. In 11 cases the membranes had been ruptured from forty minutes to 56½ hours. Nine patients were in labor, 3 less than six hours and 6 more than six hours. One patient had a temperature of 37.5° C. or more on the day of operation.

TABLE IV. ST. LOUIS MATERNITY HOSPITAL. CESAREAN SECTIONS, LOW CERVICAL

Total cases by this method				66
CULTURES:				47
Longitudinal				NEGATIVE
POSITIVE				NEGATIVE
Aer. Mixed Anaer.				NEGATIVE
Receiving acriflavine in glycerin		17	Aer. Mixed Anaer.	42
(Face)(Bag) (Intra partum)				
Not receiving acriflavine in glycerin		2		2
				(1 merthiolate and glycerin)
Elective				39
Afebrile				39
Ruptured membranes				31
Extremes—1½ to 89¾ hours				
In labor				34
Extremes—2¼ to 107½ hours (4 less than 6, 30 more than 6 hours)				
Vaginal examinations				28
Excellent healing of wound				51
DeLee shuttle: Longitudinal, 2; Transverse, 22; Total				24
Deaths				0
Temperature: 37.5° C. or more on day of operation				9
2 cases attempted forceps delivery before section, 1 bag induction.				
Considered afebrile if cause of fever was found outside genital tract.				

Table IV shows 3 positive uterine cultures in the low cervical sections: one aerobic, with *B. coli* present after a labor of forty-eight hours with ruptured mem-

antiseptic vaginal instillations as a means of prevention of such contamination appears to be most rational.

TABLE I. JOHNS HOPKINS HOSPITAL  
(Reported by J. W. Harris and J. H. Brown, 1927)

Total uterine cultures		50	
Analysis			
Negative		28	
Positive		22 (44%)	
(Anaerobic growth		45%)	
Classical sections	31	Low cervical sections	13
Analysis		Analysis	
Negative		Negative	
Positive		Positive	
(Anaerobic growth, 50%)		(Anaerobic growth, 50%)	
		Radical sections	
		Analysis	
		Negative	
		Positive	
		(Anaerobic growth, 20%)	

The findings of Harris and J. H. Brown<sup>1</sup> on the service at Johns Hopkins Hospital are shown in Table I. Vaginal preparation was not practiced in this series of 50 cases and positive uterine cultures were obtained in 22 cases at the time of section (44 per cent). Anaerobic growth was noted in 45 per cent of the positive cultures, emphasizing again this group of organisms as the chief offenders. Their conclusion was that, "no sterile cultures were obtained from patients in whom active labor had lasted for six hours or more and only one positive culture was obtained where labor had progressed less than six hours." After six hours of labor they suggested the use of the low cervical section or the radical procedure (supravaginal hysterectomy). May we not use these results as a control group to compare with the present series in which vaginal instillations were consistently used as a part of the routine preparation?

TABLE II. ST. LOUIS MATERNITY HOSPITAL  
(Jan. 1, 1931 to Jan. 1, 1939)

Total uterine cultures		144	
Analysis			
Negative		138	
Positive		6 (4.1%)	
(Anaerobic growth, 83%)			
Classical sections	47	Low cervical sections	66
Analysis		Analysis	
Negative		Negative	
Positive		Positive	
(1 Intra-partum infection, mixed)		(1 Intra-partum infection)	
Anaerobic growth, 100%		Anaerobic growth, 66%	
		Radical sections	
		Analysis	
		Negative	
		Positive	
		(Intra-partum infection)	
		Anaerobic growth, 100%	

Table II gives the results obtained in a series of 144 uterine cultures on the service of the St. Louis Maternity Hospital. All but 10 of these patients received the aerisavine instillations routinely. Only 6 positive cultures were found, an incidence of 4.1 per cent. This is but one-tenth the incidence noted in the study from Johns Hopkins Hospital. Anaerobic growth was present in 83 per cent of the positive cultures. A pure aerobic culture was obtained in one instance of a face presentation which had been in labor for forty-eight hours with ruptured membranes for the same length of time. *B. coli* was grown on the culture. There were no complications in this case. Intra-partum infection was present in 3 (50 per cent) of the patients with positive uterine cultures.

Table VI reports 144 uterine cultures obtained in 274 sections performed, or 52.5 per cent. Of the 6 positive cultures obtained, 1 was elective and 5 were not. Three cases were intra-partum infections in which the infection was present before the instillations were started. One death occurred among the cases cultured, and it was due to hemorrhage. Nine of the 10 cases not prepared with the instillations were elective sections which would likely not be contaminated, although an anaerobic culture was obtained in one instance. A total of 35 cases were not elective and only 5 of these patients were found to have positive cultures (14 per cent).

TABLE VII. ST. LOUIS MATERNITY HOSPITAL

(Jan. 1, 1931 to Jan. 1, 1939)

Total deliveries	12,579
Total deaths	44 (1—285)
Corrected deaths	35 (1—359)
Total sections	274 (1—45)
Total deaths in section cases	6 (1—2096) (1—45 sections)
Analysis as to cause	
Infection, puerperal	3* (year 1931)
Hemorrhage	1
Toxemia	1
Cardiac	1

\*Puerperal infection was accountable for 50 per cent of the deaths and each of these deaths occurred during 1931, when the use of acriflavine instillations was in the experimental stage.

Table VII gives total deliveries, deaths, and sections. No death from puerperal infection has occurred in 12,579 deliveries, except the 3 deaths associated with delivery by cesarean section. The deaths following cesarean section are analyzed, and it is shown that puerperal infection was accountable for 50 per cent of the deaths and each of these 3 deaths occurred during the year 1931, when the use of acriflavine instillations was in the experimental stage. Since 1931, this most important cause of mortality associated with cesarean section seems to have been brought under control. Intra-partum infections may still occur and be the cause of considerable anxiety.

Adair<sup>9</sup> states that, "Actual genital infection of the parturient woman has been considered a contraindication to any type of cesarean section except in case of the absolute indication when it should be associated with a hysterectomy or Porro operation. The absolute indication for cesarean section exists when it is not possible to deliver either a living or a dead baby through the parturient canal without serious damage or danger to the mother.

"We recognize parturient cases with potential or actual genital infection. In the potential group we place those patients who have been exposed to genital infection by vaginal examination or manipulation during labor, those who have been in labor twenty-four hours or longer, and those in whom the membranes have been ruptured twelve to twenty-four hours or longer. We do not perform any type of cesarean section on these patients if they can be delivered through the natural passages with relative safety to the mother and baby. Where the exposure has been considerable, a Porro hysterectomy may be a necessary sequence to an indicated cesarean section.

"The actually infected patients include those who present clinical and laboratory evidence of an infection with or without localizing genital findings. In the latter group those without findings which locate an infection as extragenital are regarded as having a genital infection. Our opinion is that all actual infection is still a contraindication to cesarean section. The only indication for cesarean section in these cases is the absolute one, i.e., where a dead fetus cannot be delivered even by craniotomy through the parturient canal. When a cesarean section is necessary, we believe a hysterectomy is a necessary sequence.

branes and a face presentation; 1 mixed (aerobic and anaerobic) in a patient in labor twenty-four hours with membranes ruptured thirty hours and bag induction attempted; 1 anaerobic intra-partum infection. A negative uterine culture was obtained in an elective section in which an instillation of merthiolate in glycerin was substituted for the acriflavine instillation. The membranes were ruptured in 31 patients from 1½ hours to 89¾ hours. In 34 patients labor had been in progress from 2¼ hours to 107½ hours, 4 less than six hours and 30 more than six hours. In 2 patients forceps delivery was attempted before cesarean section was performed, and in each, the uterine culture was negative. Nine patients had temperatures of 37.5° C. or more on the day of operation.

TABLE V. ST. LOUIS MATERNITY HOSPITAL. CESAREAN SECTIONS, RADICAL

Total cases by this method			31
POSITIVE CULTURES			Negative CULTURES
Receiving acriflavine in glycerin	Aerob. Mixed Anaer.—1 (Intra partum)		29
Not receiving acriflavine in glycerin	Aerob. Mixed Anaer.		1
Elective			28
Afebrile			21
Ruptured membranes			4
Extremes—10 hours to 2 weeks			
In labor			4
Extremes—1¼ to 79 hours (1 less than 6, 3 more than 6 hours)			
Vaginal examinations			7
Excellent healing of wound			21
Deaths (hemorrhage)			1
Indications for removal of uterus	{Sterilization 25 Myoma 6}		31
Temperature: 37.5° C. or more on day of operation			1
Considered afebrile if cause of fever was found outside of genital tract.			

Table V has one positive uterine culture in the radical sections. This was anaerobic and in an intra-partum infection. In 4 patients the membranes were ruptured for from ten hours to two weeks before operation. Four patients were in labor from 1¼ hours to 79 hours, 1 less than six hours and 3 more than six hours. One death resulted in this group of cases because of hemorrhage from a pedicle. The indications for removal of the uterus were: sterilization in 25, and myoma in 6. One patient had a temperature of 37.5° C. or more on the day of operation.

TABLE VI. ST. LOUIS MATERNITY HOSPITAL

Total uterine cultures Jan. 1, 1931, to Jan. 1, 1939		144(52.5%)	
Analyses of cultures			
Negative		138	
Positive		6 (1 elective)	
Aerobic	1	Mixed	2
( <i>B. coli</i> )		(1 Intra partum)	
Anaerobic growth		83%	
Deaths in cases cultured		1	
Cause			
Infection		0	
Hemorrhage		1	
		NEGATIVE	
		POSITIVE	
134 patients prepared with acriflavine		129 (100 elective)	5 (not elective)
10 patients not prepared with acriflavine		9 ( 8 elective)	1 (elective-anacrobe)
35 patients were not elective and only 5 of these had positive cultures (14%)			

## CONCLUSION

Antiseptic vaginal instillations offer a means of preparation of a patient for cesarean section which will (1) largely eliminate one of the most important causes of mortality, infection; (2) reduce the incidence of positive uterine cultures obtained; (3) make it relatively safe to postpone operation until a much later hour in labor; and, (4) lower the indication for the more radical operative procedures. Of course, intra-partum infection may occur and this can only be prevented by the earlier prophylactic use of the instillations.

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DISCUSSION ON THE PAPERS OF DRS. MATTHEWS AND ACKEN,  
AND BROWN

DR. FRED L. ADAIR, CHICAGO, ILL.—My report from the service of the Chicago Lying-in hospital covers 500 cesarean sections. Tubal ligation was practiced in about 36 per cent of these cases, most of which were repeat sections.

Table I shows the types of operations and Table II the indications for the sections.

TABLE I. TYPES OF OPERATIONS

	PER CENT
279 Laparotrachelotomies	55.8
183 Laparotrachelotomies and sterilization	36.4
30 Porro cesarean sections	6.0
8 Classical cesarean sections (Four sterilized)	1.6

TABLE II. 500 CESAREAN SECTIONS

	CASES	PER CENT
<i>Indications (Major Factor):</i>		
Contracted pelvis	200	40.0
Pre-eclampsia	44	8.8
Placenta previa	40	8.0
Previous cesarean section	39	7.8
Cardiac disease	35	7.0
Abruptio placentae	25	5.0
Dystocia dystrophy syndrome	22	4.4
Chronic nephritis	20	4.0
Cervical dystocia	12	2.4
Cephalopelvic disproportion	10	2.0
Eclampsia	8	1.6
Previous repeated stillbirths	8	1.6
Fibromyoma uteri	5	1.0
Miscellaneous	30	6.0

Cultures were taken on most of these cases in conformity with our routine procedures for all abdominal operations. The main objective of our three culture

"... We have records of 20 Porro operations in infected cases. Of these there were 12 potential and 8 actual infections. There were additional indications for hysterectomy in many of these patients. There was no mortality in our series."

In our series 23 patients (15.9 per cent) were in labor twenty-four hours or longer. Culture of the uterus was negative in 18 of these cases (an incidence of 78.2 per cent). Five cases were found to have positive uterine cultures after being in labor for this period of time: three of these were intra-partum infections; 1 had a bag induction; and, 1 was a brow presentation in a myomatous uterus. The mortality was nihil.

The 3 patients who died as the result of puerperal infection occurred early in this study (1931). Culture of the uterus was not obtained in each instance. The first patient received 1 instillation and then had an emergency section for rupture of a previous cesarean scar. Temperature was normal on admission. *Staphylococcus albus* was found on blood culture, wound culture, and later on uterine culture. The second case had normal temperature on admission. An instillation was given once a day for five days before operation. Blood culture showed *Streptococcus hemolyticus*. A previous cesarean section had been done on this patient a year and a half previously with no morbidity. The third case was one of intra-partum infection. Four instillations were given. Two days postoperatively the patient's husband informed us that a midwife had examined the patient several times before admission to the hospital. Peritoneal culture showed a mixed culture (aerobic and anaerobic organisms).

#### SUMMARY

1. In a report from Johns Hopkins Hospital, 44 per cent positive uterine cultures were found without the use of instillations.

2. In our series, 4.1 per cent positive uterine cultures were obtained with the routine use of acriflavine instillations.

3. The importance of anaerobic organisms as the chief contaminants is stressed.

4. With the use of antiseptic instillations the period of time in labor may be greatly prolonged with negative cultures being obtained as late as 107½ hours after the onset of labor.

5. Intra-partum infection may be present on admission and vaginal instillations are too late to be of real value.

6. Among the patients cultured there was one death which resulted from hemorrhage.

7. Fifty-two and five-tenths per cent of the patients who had cesarean sections were cultured.

8. Of the 6 positive cultures, 5 were not elective cases.

9. Thirty-five cases were not elective and only five of these patients had positive cultures (14 per cent).

10. Positive cultures can be obtained with membranes intact.

11. The morbidity in this series was 52.8 per cent.

12. Three deaths from puerperal infection occurred during the first year of the study.

13. Instillations should be given prophylactically twice daily on waiting cases and every four hours if in labor.



The tables following will show the number and percentage of positive and negative cultures and the organisms which were found in the different series. Table IV shows the percentage of different organisms from Culture I, found in those cases where positive cultures were obtained. Table V shows similar data from Culture II and Table VI shows similar data for Culture III. Table VII shows the percentage of negative cultures obtained in all cases and the percentage of all cases in which various organisms were found by Culture I. Table VIII shows similar data for Culture II and Table IX shows similar data for Culture III.

TABLE VI. CULTURE III

	CASES	PER CENT OF POSITIVE
G. gram + diplobacillus	88	26.99
<i>Staph. albus</i>	75	23.00
Gram + diphtheroids	63	19.35
<i>Strep. diplobacillus</i>	24	7.36
Döderlein's bacillus	17	5.21
Anaerobic strep.	13	3.99
<i>B. subtilis</i>	9	2.76
<i>B. mesentericus</i>	9	2.76
Gram + rods	9	2.76
<i>Strep. hemolyticus</i>	8	2.44
<i>B. coli</i>	4	1.22
<i>Strep. proteus</i>	2	0.61
Miscellaneous	4	1.22

TABLE VII. CULTURE I

	CASES	PER CENT OF ALL
Negative	357	71.11
L. gram + diplobacillus	36	7.11
<i>Staph. albus</i>	33	6.57
Gram + diphtheroids	19	3.78
<i>Strep. diplobacillus</i>	12	2.37
Anaerobic strep.	9	1.79
<i>Strep. hemolyticus</i>	8	1.59
Döderlein's bacillus	7	1.39
<i>B. subtilis</i>	5	1.00
<i>B. mesentericus</i>	4	0.80
Gram + rods	3	0.60
<i>B. proteus</i>	2	0.40
Nonhemolytic strep.	2	0.40
Miscellaneous	4	0.80

TABLE VIII. CULTURE II

	CASES	PER CENT OF ALL
Negative	363	72.60
L. gram + diplobacillus	35	7.00
Gram + diphtheroids	25	5.00
<i>B. mesentericus</i>	22	4.40
<i>Staph. albus</i>	18	3.60
Anaerobic strep.	7	1.40
<i>Strep. diplobacillus</i>	6	1.20
Döderlein's bacillus	5	1.00
Gram + rods	5	1.00
<i>B. proteus</i>	3	0.60
<i>B. prodigiosus</i>	3	0.60
<i>B. subtilis</i>	3	0.60
<i>Strep. hemolyticus</i>	3	0.60
Miscellaneous	2	0.40

techniques was to determine the presence and time of contamination during an abdominal operation. The following method was followed in making our I, II, III cultures (Table III).

TABLE III

*Culture I*

The first culture was taken after the incision was made down to the peritoneum. Organisms found, after having been cultured, were introduced from any one or more of the following sources: instruments, instrument table, drapes, gloves, operator, operating assistants, abdominal skin after preparation with benzene, ether, iodine, alcohol, etc.

*Culture II*

The second culture was taken immediately after the peritoneum was nicked. This culture denoted what organisms were present in the peritoneal cavity.

*Culture III*

The third culture was taken in the operative field immediately before closure of the peritoneum. Organisms usually found are those that were found in both Culture I and Culture II, in addition to any intrauterine, cervical or vaginal organisms.

TABLE IV. CULTURE I

	CASES	PER CENT OF POSITIVE
<i>L.</i> gram + diplococcus	36	24.81
<i>Staph. albus</i>	33	22.75
Gram + diphtheroids	19	13.10
<i>Strep. diplobacillus</i>	12	8.27
Anaerobic strep.	9	6.20
<i>Strep. hemolyticus</i>	8	5.52
Döderlein's bacillus	7	4.55
<i>B. subtilis</i>	5	3.42
<i>B. mesentericus</i>	4	2.76
Gram + rods	3	2.07
<i>B. proteus</i>	2	1.38
Nonhemolytic strep.	2	1.38
Miscellaneous	4	2.76

TABLE V. CULTURE II

	CASES	PER CENT OF POSITIVE
<i>L.</i> gram + diplobacillus	35	25.54
G. + diphtheroids	25	18.24
<i>B. mesentericus</i>	22	16.05
<i>Staph. albus</i>	18	13.13
Anaerobic strep.	7	5.10
<i>Strep. diplobacillus</i>	6	4.43
Döderlein's bacillus	5	3.64
Gram + rods	5	3.64
<i>B. proteus</i>	3	2.18
<i>B. prodigiosus</i>	3	2.18
<i>B. subtilis</i>	3	2.18
<i>Strep. hemolyticus</i>	3	2.18
Miscellaneous	2	1.46

In the repeat cesarean sections 5 of 11 deaths were due to intestinal obstruction, a complication which I have never met in a large series of repeated low flap operations.

Throughout the paper one is impressed with the fact that the serious infectious complications followed the classical section and that there were no deaths from sepsis in the lower segment operations. Again, fewer deaths occurred in the hands of men of greater experience than in those of younger men. This is as it should be with any form of surgical operation.

Spinal anesthesia was used in 90 cases, and the authors state that "Many clinics would do well to use it more frequently." Personally I feel that spinal anesthesia is the most dangerous form of anesthesia in cesarean section. This statement is based on facts and not on impressions. Local anesthesia may be used in all instances where spinal might be indicated and this with a marked increase in safety.

Edward A. Schumann has shown in a paper recently published in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY that the mortality and morbidity could be markedly reduced if the operator could make up his mind to interfere early even though this might entail the performance of a few more cesarean sections. He states, "I have never regretted doing a cesarean section, but I have regretted not doing one."

The gross fetal mortality is given as 5.2 per cent. This is within ordinary limits, but shows none the less that abdominal delivery does not necessarily assure a living baby.

The best figures from the standpoint of mortality which I have been able personally to obtain gave a gross maternal mortality of 1.6 per cent in a series of 429 transverse cervical cesarean sections, and a gross fetal mortality of 2.5 per cent in the same series.

It is evident from Brown's important statistics that the instillation of antiseptics in the vagina, 1 per cent neutral acriflavine in glycerin, will definitely reduce morbidity and mortality in cesarean section. Matthews and Acken, as well as Brown, have reported similar results by the instillation of mercurochrome. Strangely enough, during my training at the Carney Hospital, I was taught meticulously to prepare the vagina before a panhysterectomy and at the New York Lying-In Hospital never to do vaginal manipulations of any kind before performing cesarean section. In view of Brown's findings, I am convinced that I will change my method of procedure in this regard.

DR. ACKEN (closing).—I should like to stress that we have instilled vaginally an ounce of 4 per cent mercurochrome every twelve hours during labor. It has not entirely eradicated sepsis but has reduced it. We agree with Adair's statement that the technique of instillation must be carried out with great care.

We accept Phaneuf's criticism concerning patients who have had a previous gynecologic operation. These patients should not be subjected to a long test of labor.

DR. ARTHUR H. CURTIS, CHICAGO, ILL.—If the instillation of a solution in the vagina decreases the incidence of infection, why not make the vaginal preparation such as is ordinarily made for abdominal hysterectomy? It would seem to me to be much more thorough and more clean.

DR. HENRY S. ACKEN, JR.—We assume that there has been no gross contamination of the vagina before delivery, and we use the mercurochrome instillation simply as a means of eradicating such infection as may have entered from the outside.

DR. BROWN (closing).—The same method of obtaining the culture was used as that described by Harris and Brown: "All of the cultures were taken through the uterine incision in order to ensure that they could not be contaminated by the vaginal secretions. As soon as the child was delivered, before the hands or the instruments had been introduced into the lower uterine segment, a sterile cotton

I would like to stress that, while we do not use vaginal instillations as a routine procedure, the aeriflavine and glycerin mixture is used when vaginal examinations are made. Many of our patients who had cesarean sections had no vaginal examinations and consequently instillations were not used. Our cultures indicate that infection may be introduced through the incision as well as through the vagina. The vaginal instillations could not possibly prevent introduction of infection through the abdominal route. Another point which should be emphasized as an argument against

TABLE IX. CULTURE III

	CASES	PER CENT OF ALL
Negative	184	36.07
<i>L. gram + diplobacillus</i>	88	17.45
<i>Staph. albus</i>	75	14.70
Gram + diphtheroids	63	12.35
<i>Strep. diplobacillus</i>	24	4.71
Döderlein's bacillus	17	3.33
Anaerobic strep.	13	2.54
<i>B. mesentericus</i>	9	1.76
<i>B. subtilis</i>	9	1.76
Gram + rods	9	1.76
<i>Strep. hemolyticus</i>	8	1.56
<i>B. coli</i>	4	0.78
<i>Strep. proteus</i>	2	0.40
Miscellaneous	4	0.78

the performance of cesarean section after a long duration of labor is the one of trauma and exhaustion. I am opposed to eliminating the contraindication of the duration of labor from consideration in performing cesarean sections, and I do not believe that routine use of vaginal instillation would overcome this objection. I am opposed to the performance of cesarean section after a woman has been in labor over twenty-four hours either with or without previous rupture of the membranes. I do not believe that in general we can operate as safely and perform a cesarean section twenty-four hours after the onset of labor even with the routine use of vaginal instillations. Our figures for febrile morbidity and mortality are very low without the use of vaginal instillation as a routine procedure. These figures have been reported by Daily in a recent article on 1,000 cesarean sections performed at the Chicago Lying-in Hospital.\*

DR. LOUIS E. PHANEUF, BOSTON, MASS.—Matthews and Acken have reported in 1,000 cesarean sections, a maternal mortality of 3.18 per cent. A lower mortality throughout the series is shown for the so-called low flap or lower segment operation. This is in keeping with other published series of the last two decades. Of particular significance are the figures demonstrating no maternal mortality in secondary low flap operations and the same mortality rate in secondary classical as in primary classical sections. Furthermore, the essayists show that during the last six years of the study there was a definite decrease in mortality in the so-called cervical cesarean section but an increase in mortality in the case of the corporeal hysterotomy.

A high mortality rate was reported in patients who had had previous gynecologic operations as these women were operated upon late in labor. Most of the dystocia resulting from former gynecologic interventions are consecutive to procedures employed on the cervix uteri, especially amputation of the cervix. Every obstetrician of experience knows that this form of cervical dystocia is difficult to overcome and that cesarean section should be resorted to early, since many hours of labor will not change the condition of the cervix, if a few hours of real labor have not softened and begun to dilate the organ. Cesarean section of election or early cesarean section should show a very low mortality in this group of cases.

\*Cesarean Section. An Analysis of 1,000 Consecutive Operations. AM. J. OBST. & GYN. 37: 348, 1939.

## THE GLYCOSURIAS OF PREGNANCY\*

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*(From the Obstetric Service of the Presbyterian Hospital)*

THIS report consists of the impressions gained from our experience during the care of 43 pregnancies occurring in 38 diabetic patients, and 25 pregnancies in the benign type of glycosuria. These impressions are the summation arrived at by the cooperative study between the diabetic service of Dr. R. T. Woodyatt, his associate Dr. Leo Campbell, and the entire obstetric service of the Presbyterian Hospital, Chicago. The period of this analysis extends from 1921 to April, 1939.

This study was undertaken to evaluate our present methods of treatment and to determine whether a comparison of the histories of the diabetic patients with those of the nondiabetic glycosurias of pregnancy might not throw further light on some of the general principles underlying both conditions.

In view of recent basic observations in the fields of endocrinology and metabolism, these comparisons suggest new approaches to the problems of the glycosurias in the pregnant woman. The degree and rapidity of changes in glandular function during pregnancy in women produce an experimental subject that is much more intriguing than it is in the usual laboratory animal. Correlation and interpretation is, of course, more complicated and hazardous in the human being.

A survey of the antecedents of diabetics reveals a high incidence of glandular stigmas. The predominating type found among this group of mothers is that of the short individual who is spoken of familiarly in obstetric circles as belonging to the dystrophy syndrome. A study of the sizes and weights of the infants substantiates the findings of many other observers that at least diabetics and probably also the benign glycosurias are more likely to give birth to larger babies than do normal women. Approximately 60 per cent of the infants born to the diabetic mothers weighed 8 pounds or over. The largest one weighed 14 pounds 4 ounces, the smallest, which was premature, 4 pounds 5 ounces. A similar increase in the size of the fetus was noted in the nondiabetic glycosurias, although 10 pounds was the largest infant in this latter group. Heretofore we have ascribed the increased size of the baby largely to the hyperglycemia of the diabetic mother. This explanation, however, cannot be valid in the benign types of glycosuria, in which the blood sugar level is usually somewhat below normal. In like manner, if we review the previous obstetric histories of the group of diabetic women, we find that they also gave birth to a

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covered swab was passed through the uterine incision and rubbed over the uterine segment, care being taken that it did not come in contact with any portion of the uterus except that from which the culture was desired.''

I might also say that the instillation that we use in preparation for cesarean section is that used routinely in all of our patients in labor. Actually it started as a routine preparation during labor. I would urge Matthews and Aiken to use these instillations a little more frequently, because in checking up on the cultures of the vagina after instillations, I find that it takes from eight to ten hours for the solution to give us an actually sterile culture from the vagina. We have observed infections sometimes when the patient has been in labor for only a couple of hours after the instillation was first given. Such a patient has not received adequate care in that period of time.

It has been rather definitely proved that the inheritance ratio of the diabetic tendency is high. Priscilla White has reported it at 52 per cent. She has also reported that 90 of 100 children were above average height before they became diabetic. Fundamental clinical observations as well as animal experimentation have definitely localized the impetus to somatic growth in the anterior lobe of the hypophysis. We do not see rapidity of growth illustrated as well anywhere else in animals or man as in the pregnant female. The amazing growth of the fetal elements is almost matched by the tremendous hypertrophy of the uterine apparatus. Even the accessory organs of reproduction, such as the breasts, respond to this stimulus. In addition we have the more incompletely defined pituitary functions which include carbohydrate and fat metabolism other than by the way of the thyroid, pancreas or adrenals. The recent isolation by Collip and his co-workers of a potent metabolic factor from the pituitary may be important in this general problem. May some of this change not be due to the protective slowing of the sex glands during pregnancy? A similar or appreciable gain in weight occurs regularly in the castrate or following the climacterium in both men and women. This depression of the sex glands is for the most part probably due to the increased activity of the pituitary gland. In future studies additional information is desirable and a complete family history should be obtained as far back as information is available. This history should include not only the details of familial diabetes but all evidence of glandular disease or dysfunction. Still closer controls would include the extension of family histories to include the past obstetric histories of all branches of the family tree. We have now in the hospital a fourteen-year-old boy in whom diabetes was discovered four months ago. The family history for three generations back does not reveal diabetes but a surprising number of giant fetuses and stillbirths. The average weight of our diabetic mothers at term was 159.5 pounds. Several of them weighed over 200 pounds and two reached a weight of 240 pounds. In the nondiabetic group 13 of them weighed from 160 to 225 pounds. Twelve of them weighed from 109 to 142 pounds.

Recent clinical observations by many observers have indicated that the fundamental factors controlling glandular balance may also be closely connected with the pregnancy toxemias. Marked or too rapid gains in maternal body weight frequently seem to coincide with the development of toxic states. Transient glycosurias developing during the latter half of pregnancy are often soon followed by the appearance of edema, hypertension and albuminuria. This observation was made first by Williams, and we have noted it frequently in our patients. This type of transient glycosuria is not included in the present series. In spite of the fact that no specific pancreatogenic hormone has been isolated from the pituitary, experiments, such as those initiated by Houssay, indicate that the pituitary is most intimately associated with the glycogenic equilibrium. There is a growing belief that eventually the control of a considerable number of diabetics and perhaps benign glycosurias will be carried out with other hormonal substances rather

high percentage of giant babies *long before their clinical diabetes had become manifest*. The gain in maternal weight during these previous pregnancies, where recorded, corresponded with the gains in weight during our period of observation. Previous published clinical reports indicate that maternal dietary changes have no appreciable effect on the weight of the infant during normal pregnancy. When we compare the gain in weight of the mother directly with the weight of her baby in these groups, we find that in general the mothers who gained the most weight during pregnancy more frequently gave birth to the largest babies (Chart 1). This was particularly noticeable among the diabetics, although to a lesser extent in the nondiabetic patients. In the diabetic group, all but one of 19 mothers who weighed 150 pounds or over gave birth at term to babies weighing 8 pounds or more. More information should be acquired concerning the transmission of glucose and fat through the placenta. It has been our experience that the nondiabetic pregnancy, particularly the overweight toxemic individual, carries a fasting blood sugar which is consistently in the lower levels of normal. Furthermore, the blood sugar levels of the cord blood are usually only slightly over one-half of that of the mother. In one instance blood taken from the mother shortly after intravenous glucose solution was given contained 540 mg. of glucose while her baby's cord blood held only 60 mg. per 100 c.c. We expect to check these findings further, particularly in twin pregnancies and in animals. If we compare the average fetal weights of the undersized babies born to overweight toxemic mothers with the oversized infants of a like group of overweight toxic glycosurics, it would seem logical to conclude that other factors besides the mere ingestion of more food are responsible for this phenomenon, or that the toxemias are of a different type. We have ascribed the failure of growth of the baby in the toxemias of pregnancy to toxic conditions, particularly in the placenta. But many of the largest babies observed in our series were born to mothers who showed the severest symptoms of toxemia, and who had no gross changes in the placentas. In like manner we have all seen very small, poorly developed babies born to overweight toxic mothers with no abnormal gross or microscopic changes in the placenta to account for it.

Newburgh has stated that gain in body weight is in direct proportion to the increased ingestion of food. He believes that glandular imbalance has relatively little to do with the problems of loss or gain in body weight. It would seem to us that particularly in the diabetic pregnancy whose dietary regime is usually so strict and accurate, at least some of the marked gains of weight especially in the latter months of gestation might require additional explanation. What change occurs in the mechanism of appetite during normal pregnancy? Almost without exception pregnant women develop a desire for food which is beyond the immediate needs of the growing fetus. Proof of this is found in the extra maternal weight gain during normal gestation. It would seem to us that this mechanism has probably undergone even more marked derangement in this group of patients than in a similar number of normal pregnancies.



rate even for the insulin era is appallingly high. A résumé of the obstetric histories of the diabetic patients before they came under our observation records 13 stillbirths and 13 miscarriages in a total of 85 pregnancies. During our attention, while on accurate diabetic management, these 43 pregnancies ended in stillbirths six times and 7 of the abortious were done therapeutically. We cannot be greatly impressed by the fetal life-saving properties of insulin.

A critical study of our records indicates that the majority of the term fetal accidents were not due to obstetric causes. Nor, as we have already indicated, do we feel that they were directly connected with the high incidence of toxemia. It may be possible that too accurate control of the diabetes has produced a fatal hypoglycemia in the fetus, but we doubt it. All possible steps have been taken to prevent this catastrophe. These steps include the giving of glucose solution by bottle and nipple immediately after birth, as suggested by Randall, and maintaining an adequate maternal glycosuria during pregnancy. There is a great need for more detailed studies of the fetal and maternal blood sugars during the last few weeks of pregnancy, during and immediately following labor. The antenatal and intra-partum accidents to the baby were about equally divided in the diabetic group of patients. This mortality was six times as frequent as in the benign type of glycosuria. The appearance of fetal abnormalities was the same in both groups.

The insulin requirements of most if not all of our patients was increased as pregnancy progressed. It would seem that in the human female at least the production of insulin by the fetal pancreas does not usually compensate for the increased demands on the maternal organism. On the contrary, the insulin requirement often falls rapidly after labor is over. The most frequent insulin reactions in this group occurred in the first four days of the puerperium. This in large measure is most likely due to the insult of labor and delivery, but one may speculate that the same mechanism is also operating which at this same time restores normal maternal water balance and promotes the activity of the breast. One may wonder whether a negative Aschheim-Zondek test appearing at about this same time is not significant. These questions may well be asked when we study the puerperal and labor records of these patients. Judged by the usual standards there were 56 patients who had an uneventful afebrile convalescence. Three of the diabetics and one of the simple glycosurias had elevations of temperature. All of these patients left the hospital well at the usual time. It was not in this last group of patients nor in those who had the longest and more traumatic labors where the largest number of insulin reactions occurred during the puerperium.

We may speculate further on the appearance of acetone bodies in the urine of these patients. The persistence of these bodies on an adequately balanced diet, as high as 2,000 calories, for several days suggests an additional factor to that found in normal pregnancy where acetonuria may occur even with normal sugar consumption. One is reminded of the experiments of Anselmino and Hoffman who showed that alkaline

than insulin. In light of our present knowledge the pituitary seems to be the most likely candidate for this role. Approximately 70 per cent of our number of diabetics revealed evidence of one or all of the cardinal signs of the toxemia of pregnancy. The greatest proportion of these occurred in the markedly overweight individuals. All but two of these patients who showed two or more signs of toxemia weighed from 160 to 240 pounds. Many of these toxemias were of a severe degree but none, and we feel this may be important, developed the convulsive type of toxemia. Labor was not induced in any of these patients on account of toxemic symptoms. Priseilla White found 21 per cent of 168 diabetic women during the insulin era who developed signs of pre-eclamptic toxemia, only five of whom developed convulsions. These investigators feel that the diabetic woman protects herself against eclampsia by destroying the placenta and incidentally the child, which accounts for the high incidence of stillbirth and spontaneous abortion. More recent work in their clinic indicates that a rise in serum prolactin, anterior pituitary-like hormone, and a fall of estrin preceded the clinical signs of toxemias, stillbirth and often premature delivery or miscarriage. Taylor has not been able to substantiate these findings. In spite of this we feel particularly in view of Schneider's observations on the production of giant fetuses and their increased mortality in the rabbit by the use of pituitary substances, that this general direction offers the most encouraging field for study. In our series the patients who were delivered of dead babies did not present the symptoms of severe toxemia; in fact, only two of them showed either hypertension or albuminuria. One of these had a systolic blood pressure of 158 and a trace of albumin in the urine, the other a blood pressure maximum of 140 and 3 mm. of albumin. We did not find placental pathology of a degree which we felt might have caused fetal death. Furthermore, the size of the dead babies was much larger than those found with marked placental damage in the ordinary toxemia.

The type of toxemia encountered in this series of patients was predominantly nephrotic; edema was the commonest and most marked finding. Hypertension came next in frequency, although albuminuria was noted in eight of the diabetic and three of the renal glycosurias. Herriek and Tillman have noted as significant the frequent association of diabetes and the vascular type of toxemia. Diabetics in general are very likely to develop vascular lesions of a marked degree. In view of the unusually high incidence of toxic symptoms in these patients the question might be raised as to whether they are largely the result of these vascular changes, disturbances in glycolytic equilibrium or are more probably another symptom of the fundamental glandular dysfunction which also causes the glycosuria. Most accurate insulin control seems to be inadequate in preventing or allaying the symptoms of this toxemia of pregnancy.

It is quite evident from a study of the literature that insulin has accomplished relatively little in lowering the fetal death rate. The main benefit has been in lowering the number of maternal deaths to approximately the normal incidence in pregnancy. The fetal death

TABLE II. RECORD OF FETAL ACCIDENTS

CASE	AGE	DURATION DIABETES	HEIGHT MA- TERNAL WEIGHT	PREVIOUS OBSTETRICS	PRESENT OBSTETRICS
1	25	4 months B.P. 158 Albumin, trace	5 ft.-6 207.5	12 lb., normal 3 yr. ago Spontaneous abortion 2 years ago	Began labor 5:45 P.M. Break- fast, pancakes and syrup. Urine free of sugar on ad- mittance. Delivered still- born, 14 pound 4 ounce baby at 8:55 P.M. Heart tones rapidly disappeared when dilatation practically complete. Forceps delivery for failing heart tones. No obstetric cause of fetal death. First insulin, 8 units, at 12 P.M. following delivery.
2	40	3-4 mo. Sympto- matic B.P. 140/90 3 mm. albumin	238.5 280 four years ago	First husband—mar- ried at 15 1 girl, normal 1 girl, normal 1 boy, normal 1 miscarriage Second husband—7 yr. ago 1. miscarriage 2. miscarriage 3. boy, heart dis- ease O.K. 4. miscarriage 5. twins born dead	Heart tones not heard on ad- mittance. Patient having dark brown discharge. Fetus badly macerated. Had not been on insulin previously. Six months term—3 pounds 15 ounces. Insulin—8-10-10- 10. Urine 0.17-2.607.
3	27	1½ mo. B.P. 120/80 No alb.	4 ft.-11 153.5	1923, 7 lb. normal girl 1926, dead baby 1931, dead baby 1934, dead baby	Intranterine fetal death 24 hours before labor began. Cord around neck twice. Ba- by weighed 8 pounds 9 ounces. No insulin.
4	40	1½ yr. B.P. 120/92 No alb.	5 ft. 2½ 196½	1916, Stillbirth, 3 hr. labor 1917, Normal, 9½ pounds 1919, Normal In between 7 babies weighing from 8 to 10 pounds 1930, Stillbirth, 14 pounds	Normal delivery, labor 6 hr. 40 min. Insulin 16 mits. Died 3 days later, intestinal atresia, weight 10 pounds 10 ounces. Patient had severe pituitrin reaction following delivery.
5	25	3 mo. B.P. 124/90 No alb.	137	Normal delivery, 6¾ pounds, 3 weeks premature Maternal hyperten- sion and albumin- uria	Neonatal fetal death, probably several days. Eight months term.  Discharged {Prot. 14 Reg. 4 Baby weighed 9 pounds 7 ounces.
6	33	9 yr. B.P. 120/68 No alb.	146	None	Bag induction followed by ar- tificial rupture of mem- branes; three-fourths dilata- tion of cervix, sudden disap- pearance heart tones. Crani- otomy, fetus, 9 pounds; short cord, 12 inches. Insulin 22- 22-22-22; 1966 cal. Urine 2.21-48.6.
7	31	4 mo. B.P. 120/80 No alb.	165	1. 7 pounds, died at 2 mo. 2. 7 pounds, normal 3. 7 pounds, died at birth 4. 10 pounds 11 ounces, O.K.	Ante-partum fetal death, prob- ably at onset of labor. Weight 10 pounds 5 oz. Di- abetes treated 4 months of pregnancy. Insulin 4-4-4. Fetal blood sugar 0.08. Urine, 2.93-11.84.

TABLE I. LIVING BIRTHS

AGE	DURATION DIABETES MONTHS	WEIGHT	LABOR	INFANT
DIABETICS				
27	18	101	4:45	6-12
22	2	110	Spont.	6-10
32	30	120	3:30	8-5
31	84	121	14:45	7-15
26	72	130	7:45	6-12
28	114	134	6:30	4-14
27	48	135	4:30	4-5
28	120	135	20 (L.F.)	9-15
24	15	143	L. cerv. sec.	5-15
30	24	145	12	8-7
30	2	146	2	7-13
30	12	148	14	8-6
29	72	150	13	10-3
30	84	150	40 (Dulhr.)	8-5
29	60	151	7	6-2
44	192	154	Porro	8-14
27	24	160	2:30	8-5
33	17	162	4:30 (cas. oil- quinine)	9-8
24	96	163	L. cerv. sec.	8-12
24	2	170	12 (M.F.)	8-10
24	5	174	25:45	8-0
25	17	179	8:45	8-13
43	3	181	4:30	11-1
25	3	184	14	5-14 (8 mo.)
24	24	185	9:30	10-0
29	12	198	7	9-0
37	3	240	3	11-2
GLYCOSURIAS				
26				6-10
26	21 days	109	C. Sec. c. p.	
31	120	126	11	4-5
				(1 mo. premature)
19	15 days	128	7:25	8-6
28	1	128	C. Sec. (prev. sec.- c.p.)	8-15
29	3	133	5	8-12
24	1	134	5:50	7-3
29		134		6-3
24		136	13:20	8-9
39	6	139	12:30 (M.F.)	8-2
29		142	2:20	9-6
29	7 days	160	3	9-1
35	6	164	4	4-15 prem.
33		165	17	7-3
38	4	165	10	10-0
33	5	168	9:30	6-13
26	21 days	170	6:20	8-12
29		174	3:45	9-2
21	21 days	181	4 (L.F.)	8-15
28	20	184	4	8-6
23	36	195	10 (Died 23 days later)	8-1
38	9	207	4:30	7-1

TABLE IV

DIABETICS					GLYCOSURIAS				
AGE	DURATION DIA- BETES	WEIGHT	LABOR	INFANT	AGE	DURATION SUGAR	WEIGHT	LABOR	IN- FANT
<i>Stillbirths</i>									
26	3	136	7 (castor oil and quinine)	9-7	36		180		
33	108	146	38 (bag, high forceps, craniotomy)	9-0			Not delivered here		
28		153	13 (cord around neck)	8-9	20	4 ?	225		
31	7	165	18	10-5	29		134		
24	3	207	12 (midfor- ceps)	14-4					
41	18	207	6	10-10					
40	28 yr. ?	240	5	Macer- ated					
<i>Abortions</i>									
23	12	118	Hysterectomy, 6 wk.						
23	14	125	Aborted elsewhere. In- complete D. and C. D. and C., 2 mo.						
24									
24		110	D. and C., 3 mo. Died tuberculosis						
26	60	112	D. and C., 2 mo.						
29		108	Therapeutic D. and C.						
31	24		D. and C., steril., 2½ mo.						
40	38		Hysterotomy, 6 mo. Spont., 4 mo.						

In spite of the predominance of overweight babies the average length of labor in our diabetic patients was 9.3 hours, that of the benign glycosurias 7.4 hours. Spontaneous birth occurred 44 times and 6 babies were delivered with forceps in the combined group. The one craniotomy was performed to prevent maternal damage during delivery of a baby which was already dead in utero. Cesarean section was resorted to 5 times, mostly for obstetric reasons (contracted pelvis), although occasionally the increased size of the fetus was an important deciding factor. Several of the stillbirths might have been prevented by cesarean section. However, when we carefully analyze not only the present but also the past obstetric history of these 4 cases, we are impressed with several pertinent facts.

Two of the antenatal deaths occurred at eight months' gestation. Cesarean section would of necessity have had to be performed before this time to have saved these babies.

Nine of the 13 stillbirths recorded in the previous obstetric histories of the entire group occurred in 4 of the 6 patients who lost 3 babies while under our attention. These previous stillbirths, usually of large babies, occurred long before the patient had developed clinical diabetes. This fact suggests that glycosuria is only another or perhaps

extracts of the hypophysis will produce an acetoneuria. On the other hand, Houssay has shown that hypophysectomy will eliminate ketosis. Long has repeated this by removing the adrenal glands.

TABLE III

NO. OF INFANTS	WEIGHT POUNDS	PERCENTAGE
<i>Diabetic Babies Living and Stillborn</i>		
2	4- 5	6.0
2	5- 6	6.0
4	6- 7	12.1
2	7- 8	6.0
11	8- 9	33.3
5	9-10	15.1
4	10-11	12.1
2	11-12	6.1
1	14-15	3.0
<i>Glycosuric Babies Living</i>		
2	4- 5	9.5
3	6- 7	14.2
3	7- 8	14.2
9	8- 9	42.8
3	9-10	14.2
1	10-11	4.7
<i>Average Weight of 4,622 Infants Born in Presbyterian Hospital From 1930 to 1939</i>		
NO. OF POUNDS	PERCENTAGE	
5- 6	6.0	
6- 7	24.1	
7- 8	38.0	
8- 9	24.0	
9-10	7.0	
10-11	0.9	
<i>Diabetic Stillbirths</i>		
Average age of mothers		31.8 years
Average weight of mothers		179.1 pounds
Average weight of 6 infants		10.6 pounds
Average duration of disease		27.9 months
Average duration of labor		14.1 hours
Weight of infants		
1 infant	8- 9 pounds	16.6 per cent
2 infants	9-10 pounds	33.3 per cent
2 infants	10-11 pounds	33.3 per cent
1 infant	14- 4 pounds	16.6 per cent
<i>Diabetic Abortions</i>		
Average age of 8 mothers		27.5 years
Average weight of 5 mothers		114.6 pounds
Average duration of disease, 5 mothers		29.6 months
Treatment		
1 spontaneous		
5 dilatation and curettage		
1 dilatation and curettage, and sterilization		
1 hysterotomy		
1 hysterectomy		
Mortality		
1 died of tuberculosis		

complete accord with Allen that the proper treatment for the bad diabetic who has had disasters in other pregnancies is early section, primarily to forestall intrauterine death of the fetus.

Many of the fetal deaths are neonatal, occurring in the first twenty-four hours after the birth of a living fetus, and they are due to a hypoglycemia. Allweiss of the Michael Reese Hospital has demonstrated by careful studies that the hypoglycemia of these newborn infants may often be arrested with glucose injections and in that way many of the infants can be saved who might otherwise die.

DR. RUDOLPH BARTHOLOMEW, ATLANTA, GA.—Considering that diabetic patients generally show a high cholesterol content in the blood, I have a feeling that the tendency to increased toxemia and intrauterine fetal death in these cases in the latter part of pregnancy is due to changes in the placental vessels due to cholesterol.

I recall an x-ray picture of a diabetic patient, taken in the eighth month of pregnancy, which showed very distinctly the exact location of the placenta, from the arteriosclerotic changes and calcium deposits in the placental vessels. It seems to me the high incidence of intrauterine fetal death might well be attributed to the narrowing and closure of these vessels by cholesterol and calcium deposits.

In relation to the definite increase in the incidence of toxemia, as pointed out by a number of observers, it is very interesting that Hunt, Patterson, and Nicodemus fed rabbits cholesterol and subsequently allowed them to become pregnant and removed the thyroid early in pregnancy. These rabbits developed convulsions near the end of pregnancy and the placentas showed typical dark areas of acute infarction. Many of the placental vessels were almost occluded by the lipid cells beneath the endothelium. The control rabbits which were fed cholesterol but were not thyroidectomized early in pregnancy, had no convulsions or acute placental infarcts.

DR. ALLEN (closing).—We have felt that perhaps our therapeutic abortions were rather frequent. Many of them, however, were done for patients who were either too low mentally to follow accurately diabetic treatment, or even refused to do so. Some of them had a familial history of diabetes on both sides of the family.

There were no infant deaths in this series after birth. We have for quite a while followed the plan suggested by Baer of giving the fetus glucose immediately after birth and maintaining an adequate output of sugar from the mother during labor. There did not seem to be any suggestive findings in the cholesterol values in the series we examined. I think there is a difference in the cholesterol values in the rodent and in the human being. Yet with this glandular disturbance one might expect an increase in the cholesterol values in a certain number of cases.

later manifestation of a condition that may produce larger babies and sometimes kill them before birth. All but one of these last mentioned patients were mild diabetics as judged by their insulin requirements and degree of glycosuria. One had had no insulin during labor.

We would suggest, therefore, that cesarean section as a method of delivery for diabetics should probably be reserved for:

1. Strict obstetric indications.
2. Those in whom sterilization is urgently indicated.
3. Those patients in whom the previous obstetric history reveals a previous still-birth which was not due to the usual obstetric complications.

A comparative résumé also indicates that the increased tendency toward toxemia, ketosis and unstable glandular equilibrium are further evidences of a common derangement that may have its beginning in the hypophysis or vegetative nervous system.

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#### DISCUSSION

DR. WILLIAM J. DIECKMANN, CHICAGO, ILL.—It is obvious from Allen's excellent presentation that insulin is not complete replacement therapy. The non-pregnant diabetic properly treated is still subject to a higher incidence of arterial disease than the nondiabetic and may also develop the apparently specific fatty degeneration of the liver. The fetal mortality as reported by Allen and others really shows that even properly controlled diabetes in pregnancy is accompanied by a fetal mortality much greater than normal.

Our treatment has been similar to that described by Allen. We believe that the diabetic patient should be told of the seriousness of her condition. If the patient has several other children, the management of her own diabetes at times becomes quite an economic problem; therefore if the patient is seen early in pregnancy these various conditions are discussed with her and therapeutic abortion and sterilization are used freely.

The question as to what constitutes glycosuria in pregnancy is quite an important one. I have not been able to find a satisfactory definition of it in any of the textbooks or published articles. Woodward, with whom Allen has worked, has a definition for it, but to fulfill the requirements hospitalization is necessary. In March of this year 1,375 urine specimens of pregnant patients were examined and 7 per cent gave a positive reduction with Benedict's solution. These urines are fermented and if subsequent urines are also positive a glucose tolerance test is carried out. In a period of one year, 65 sugar tolerances were done in our laboratory. Only five had normal curves and negative urines. Only 19 had normal curves, but the urines always contained sugar. Sixteen of the curves were typical for diabetes. In a six-month period we had 9 pregnant diabetic patients, an incidence of 0.66 per cent as compared with the incidence of 0.1 reported by Potter and Adair. During the same period in the hospital, 1.2 per cent were found to have a nondiabetic glycosuria.

DR. JOSEPH L. BAER, CHICAGO, ILL.—There are always two patients to be considered in pregnancy. This is especially so when the woman is diabetic. I am in



(rectal or vaginal) (in addition to the usual abdominal palpation) by careful palpation of the suture lines and fontanels; (2) The diagnosis of the intern should not be accepted unless checked by a more experienced observer; (3) The diagnosis should be made as early in labor as possible and should be checked repeatedly at intervals in the labor; (4) If, when the patient was first seen the labor had progressed to complete dilatation and the presenting point was at, or near, the pelvic floor, no diagnosis except "unclassified cephalic" should be made.

Since the inception of this plan we believe we have a more accurate idea of the frequency of the various positions than ever before. We have not, of course, been able to eliminate all errors in diagnosis, but we feel that the gross error in our present figures is probably not greater than 5 per cent. It should be noted that of the total of 2,446 patients here reported, 131 are classified as "cephalic." This includes not only patients who were seen late in labor but also others upon whom the diagnosis had not been accurately made, either owing to a large caput or through paucity of examinations. It is thought that several of these were actually occiput posterior, but the diagnosis could not be accurately established.

One hundred and eighty-five patients had diagnoses of brow, face, bregma, shoulder, breech, or twins and therefore have been excluded from this discussion of occiput presentations. This leaves a total of 2,130 occiput presentations in which the diagnoses were carefully made and therefore are considered reliable for accurate classification. In each instance the direction of the sagittal suture and the position of the posterior fontanel were recorded on the chart early in labor. In a vast majority of these cases this record was made previous to six centimeters dilatation. We have considered as occiput anterior only those cases where the sagittal suture was anterior to, or exactly in the transverse, and we have similarly designated as occiput posterior only those cases where the small fontanel was actually posterior to the transverse diameter of the pelvis. We believe this classification is simpler than that more complex one where transverse positions are recognized and recorded therefore making six groups instead of four.\*

#### INCIDENCE OF POSITIONS

Our records since using this method of diagnosis and plan of classification are shown in Table I.

These figures stand in sharp contrast with those reported by others. O.D.A. in this series is decidedly the least common position, instead of ranking next in frequency to O.L.A. O.L.P. is much more common than previously noted except in

\*Our cases were so recorded, however, that a classification into the anterior, transverse, and posterior is readily available and we offer it in the table below for purposes of comparison with other authors' series.

	PRIMIPARAS	MULTIPARAS	TOTAL
O.L.A.	344	205	549
O.L.T.	214	98	312
O.L.P.	100	36	136
O.D.P.	256	123	379
O.D.T.	165	78	243
O.D.A.	44	25	69

## OCCIPUT POSTERIOR\*

### INCIDENCE, SIGNIFICANCE, AND MANAGEMENT

L. A. CALKINS, M.D., PH.D., KANSAS CITY, MO.

*(From the Department of Obstetrics and Gynecology, University of Kansas)*

THE excellent presentations on occiput posterior by Norris W. Vaux in 1930, and A. H. Bill in 1931, led us to analyze our own experience. Our attitude toward occiput posterior and our experience in its management had been considerably different. We wondered whether our failure to deliver our patients, as soon as the cervix was dilated, had resulted in a higher fetal mortality or maternal morbidity than that indicated in these two papers. We observed that the medical profession, both general practitioners and specialists, had rather suddenly acquired a certain "occiput posterior consciousness" and dread of this position. Ill-advised attempts at delivery, even before the cervix was completely dilated, were resulting in stillbirths in rather alarming numbers. Physicians were willing to accept Vaux's recommendation of version or Bill's recommendation of Seanzoni forceps, but they sometimes failed to note that in both cases interference was not recommended until the cervix was fully dilated. This "fear" of occiput posterior has resulted in four intranatal stillbirths in this present series. Interference was undertaken by the physician with the cervix only about half dilated and delivery was attempted by forceful traction with forceps extending over a period of one to three hours after which the patient was sent to our institution.

In attempting to analyze our experience we soon found that our diagnoses of position were not sufficiently accurate to permit a critical analysis. We had been reasonably careful in making these diagnoses, but there were too many instances where the examination had been made by an intern and had not been checked by a more experienced observer. In other patients the attending man had arrived rather late and, because external rotation was toward the left, had decided that the presentation must have been O. L. A. In some cases the patient had arrived at the hospital rather late in labor with the cervix considerably dilated and the head at, or near, the pelvic floor. We therefore decided that, if accurate statistics as to the incidence of occiput posterior were to be obtained, we must have a more rigid and clear-cut system for arriving at the proper diagnosis. We also realized that unless we knew accurately the incidence of occiput posterior we could not come to a rational conclusion as to the results or proper methods of management. We therefore started in 1933 to collect an accurate series of cases and have rigidly adhered to the following plan of diagnosis: (1) The diagnosis should be made by internal examination

\*Read at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

ity rate of 3.6 per cent. In 1,102 occiput anteriors there were 48 fetal and new-born deaths, a rate of 4.3 per cent, whereas in 1,028 occiput posteriors, 29 babies were lost, a rate of 2.8 per cent. Believing that occiput anterior is not actually more dangerous for the baby than is occiput posterior, we have tried to analyze this fetal mortality rate. If we exclude ante-partum deaths, we have the figures as shown in Table II.

TABLE II

	CASES	DEATHS	RATE
Occiput anterior	1084	30	2.8%
Occiput posterior	1024	25	2.4%

Among primiparas there were 677 occiput anteriors with a loss of 23 babies, a rate of 3.4 per cent; whereas in 687 occiput posteriors, 19 babies were lost, a rate of 2.8 per cent. If white primiparas only were considered, 518 occiput anteriors with 16 infant deaths showed a loss of 3.1 per cent. Twelve babies out of the 574 occiput posteriors were lost, giving a rate of 2.1 per cent, the lowest I have ever seen except that of Dr. Bill's privately conducted cases.\* The slightly more favorable fetal mortality rate for occiput posterior as indicated by these figures would not necessarily be repeated in another similar series. We believe, however, that any properly conducted series of cases will not show a rate unfavorable to occiput posterior.†

## MATERNAL MORBIDITY

We employed the American Committee on Maternal Welfare standard for computing morbidity and found 147 of the 1,102 occiput anteriors abnormal by this standard. This is a rate of 13.3 per cent. The occiput posterior cases showed very similar figures: 146 out of 1,028, a rate of 14.2 per cent. Occiput right posterior showed an identical rate with occiput left anterior. The O.L.P. cases had a somewhat higher rate, 15.6 per cent. Whether this difference is enough to be significant would seem to be open to question. Among primiparas the difference is a little greater: Occiput anterior, 14.6; occiput posterior, 17.3, the occiput left posterior presentation being again responsible for the difference. This difference is not nearly so great as that between white and colored persons. Our over-all rate for 1,092 white patients was 15 per cent; for the 272 colored patients, 19.9 per cent. If there is any increased morbidity incidental to occiput posterior, the difference is not great and it would seem to be of little practical importance.‡

\*This series is about four-fifths clinical and one-fifth private; about four-fifths white and one-fifth colored

## ‡Causes of Fetal Mortality:

Prematurity	15
Placenta previa and premature separation	14
Severe toxemia	13
Syphilis	9
Trauma	7
Anomaly	3
Prolapsed cord	2
Miscellaneous and unknown	14
Total	77

‡The types of morbidity in this series were as follows:

		PELVIC	NO DIAGNOSIS	EXTRA PELVIC	TOTAL
Primiparas	O.L.A.	9	39	35	83
	O.D.P.	7	35	31	73
	O.L.P.	7	14	25	46
	O.D.A.	0	6	10	16
Multiparas	O.L.A.	7	14	22	43
	O.D.P.	3	6	12	21
	O.L.P.	0	3	2	5
	O.D.A.	1	1	3	5

There were 4 deaths: 1 primipara, O.D.P.: G.C. peritonitis (proved at autopsy); 1 primipara, O.L.P.: temperature 104° F. on admission, eclampsia, aspiration abscess of lung (autopsy); 1 multipara, O.L.A.: admitted with broken neck from automobile accident; 1 multipara, O.D.A.: eclampsia.

TABLE I

		TOTAL
O.L.A.	939	
O.D.P.	702	
O.L.P.	326	2,130
O.D.A.	163	

Vaux's series. Presentation in the left oblique diameter occurred 489 times, as against 1,641 cases in the right oblique diameter. This is in line with previous statements. The striking thing, however, is that there are 1,028 cases of occiput posterior as against 1,102 cases of occiput anterior. In primiparas, occiput posterior actually occurred a few more times (687) than occiput anterior (677). From a strictly biologic point of view, it would hardly seem possible that occiput posterior could be a very distinct abnormality if it occurs with equal, or almost equal frequency with occiput anterior. It is our firm conviction that if diagnoses are made with the care indicated above occiput posterior will be found to occur with almost equal frequency with occiput anterior and that the four positions will occur roughly as follows:

O.L.A.	5+
O.D.P.	4
O.L.P.	2
O.D.A.	1
Total	12+

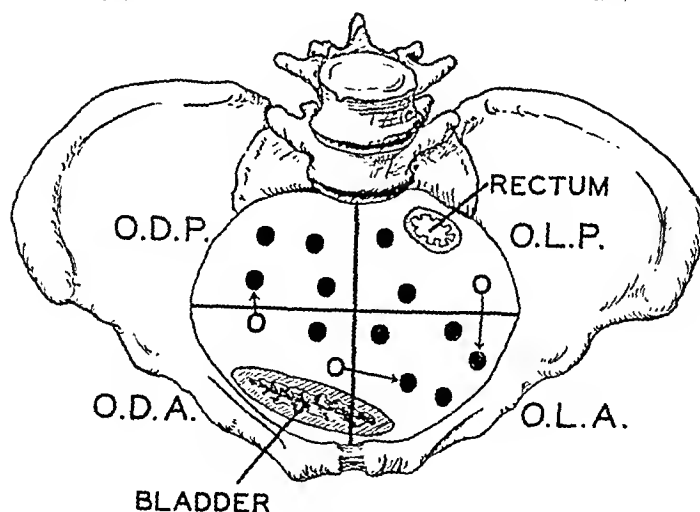


Fig. 1.

In a previous publication<sup>3</sup> we attempted to explain this relative incidence on the basis that the presence of the rectum in the left posterior quadrant of the pelvis tended to prevent the occurrence of O.L.P. in about one-third of the cases where it might, otherwise, have occurred if governed only by pure chance (Fig. 1). We further stated that the presence of the bladder in the right anterior quadrant of the pelvis tended to prevent the occurrence of O.D.A. in about two-thirds of the instances where it might have occurred were no inhibiting factor present. Dextrotorsion of the uterus may also have something to do with the more frequent occurrence of presentations in the right oblique diameter of the pelvis.

#### FETAL MORTALITY

In the 2,130 cases in this series, there were 77 fetal deaths. This figure included ante-partum deaths, as well as stillbirths and neonatal deaths. This is a fetal mortal-

forceps; 225 by low forceps; three by version; three by craniotomy. Among the occiput anteriors, there were 114 operative deliveries as against 139 among the occiput posteriors. It would seem that occiput left posterior required assistance more often than occiput right posterior.

It should be noted that the same discrepancy, unfavorable to O.L.P., was true of the length of labor (13.1 hours for the first stage, as against 12.1 hours of O.D.P.). In the last year we have learned that it is even more important to keep the bladder empty in O.L.P. presentation than in any of the other three. Perhaps if we had been more diligent in this respect as this series of cases was being observed, the average length of the first stage of O.L.P. might have been considerably reduced and fewer operative deliveries might have been found necessary. Our present attitude is that operative interference in occiput right posterior should not be more frequently necessary than in occiput anterior. If the first stage and the early part of the second stage of labor in O.L.P. be very carefully managed, operative intervention should be indicated with slightly greater frequency than in occiput anterior.

#### INTERNAL ROTATION

*Primiparas.*—Spontaneous internal rotation occurred in 539 of the 563 O.L.A.'s (95.7 per cent). Two of the remaining 24 patients delivered spontaneously without rotation. In 4 patients, median forceps rotation and delivery and in the other 18 low forceps rotation and delivery were the procedures used. In not all of these could it be said that the position "persisted." In one patient delivery was done after the patient was in the second stage only twelve minutes, and another had only fifteen minutes of second stage pains. In the majority of these 22 operative deliveries, the patient had been in the second stage at least one hour and in a few cases much longer. It would seem logical to state that in this series failure of spontaneous internal rotation occurred in about 4 per cent of the O.L.A. presentations. In O.D.A. six patients failed to produce spontaneous internal rotation. Three of these were delivered spontaneously and the others with low forceps rotation and delivery. The shortest second stage was thirty-three minutes and 3 of the 6 patients were in the second stage more than one hour, the longest being a neglected case with five hours of second stage pains. Again, fully 4 per cent failed to exhibit spontaneous internal rotation.

In the O.D.P. cases, 410 of the 437 patients had spontaneous internal rotation, 93.8 per cent. Of the remaining 27 patients, 8 delivered spontaneously with the occiput posterior. The second stage (in these 8) varied in length from twenty-two minutes to two hours and twenty minutes. Six of the 8 patients had second stages of one and one-half hours or less. The remaining 19 patients were delivered by operative procedure: Six median forceps and 13 low forceps. It should be noted, however, that one of these patients was delivered after only three minutes in the second stage and 2 others after only thirty minutes. Two babies in this group were lost; one had been dead several days before the onset of labor and the other was in a patient with complete placenta previa. There was no difficulty in the labor of this latter case. Low forceps were used to lift the head over the perineum after a seventy-nine-minute second stage. Careful study of these 27 unrotated occiput right posteriors would seem to indicate that "persistent" occiput posterior on the right side occurs in about  $4\frac{1}{2}$  per cent of primiparas, and in one-third of these spontaneous delivery can be expected after a relatively short second stage.

In the O.L.P. patients, 19 (8.0 per cent) of the 236 patients either delivered spontaneously in the posterior position (six instances) or were delivered by operative procedure before internal rotation had taken place. One of these was median forceps and the other 12 were low forceps. Three of these patients had been in the second stage less than one-half hour and delivery was undertaken because of disturbance of the fetal heart. Approximately 6 per cent, then, of occiput left posterior in primiparas either failed to undergo spontaneous internal rotation or were delivered before such rotation had taken place. Nearly half of these were delivered spontaneously and there was only one fetal death in this group. The

## LENGTH OF LABOR

*Primiparas.*—The average length of the first stage of labor for occiput anteriors was 10.8 hours; for occiput posteriors 12.5 hours. This is a very definite difference, but considerably less than the figures usually quoted. Williams<sup>4</sup> also felt that the difference is small. Careful inspection of these data further reveals that a large part of this difference in the averages is due to the fact that a first stage labor prolonged beyond twenty-four hours was more common in occiput posterior than in occiput anterior. Thirty-seven of our 668 occiput anteriors had a first stage of twenty-four hours or more (5.5 per cent of the cases); whereas 58 of the occiput posteriors had a similar prolongation of the first stage (8.6 per cent). We offer no explanation of the greater frequency of prolonged first stage at this time, for it will require considerable further study. If we eliminate these instances of prolonged labor, we find the average of the remaining 631 occiput anteriors to be 9.6 hours, and the 615 occiput posteriors 10.1 hours. This small difference of one-half hour could hardly be considered to be of very great clinical importance. The second stage showed a small comparative difference between occiput anterior and occiput posterior. Of the 554 occiput anteriors delivered spontaneously, the average duration of the second stage of labor was 51.9 minutes, while the average for the 534 occiput posteriors delivered spontaneously was 65.3—a difference of about thirteen minutes. Here again, however, we noted that prolongation of the second stage beyond two hours was more common in occiput posterior (52 instances) than in occiput anterior (25 instances). It would seem that “poor labor pains” is the most frequent explanation of prolongation of the second stage, but it is our impression at present that there are other factors which should also be considered. If we eliminate these few cases of prolonged second stage, the average of the occiput anteriors is 47.2 minutes and of the occiput posteriors, 52.8, a difference of only five and one-half minutes, which is a negligible quantity.

*Multiparas.*—The average duration of the first stage in occiput anterior was 6.8 hours; in occiput posterior, 7.7 hours. This difference of about one hour seems to be quite constant and the explanation is not to be found in the incidence of prolonged labor. There were only nine instances in which the first stage exceeded twenty-four hours in occiput posterior. The duration of the second stage of those spontaneously delivered (all but 30 of the 736 cases) was 19.6 minutes in occiput anterior and 24.6 minutes in occiput posterior, a difference of five minutes.

In primiparas therefore, occiput posteriors have a first stage about one and one-half hours longer than occiput anteriors and cause a second stage prolongation of about thirteen minutes. In multiparas the first stage is one hour longer, and the second stage five minutes longer. At least part of the reason for the longer average first stage in primiparas is the fact that truly prolonged labor (more than twenty-four hours) is more common in occiput posterior.

## OPERATIVE DELIVERY

The number of operative deliveries in our multiparas was too small to permit any accurate analysis. Among the primiparas we have been perhaps too liberal in the use of low forceps and stand ready to accept any criticism on that score. Among the 1,364 primiparas there were fifteen cesarean sections, all done for elective reasons and in no instance because of the presentation. Of 1,341 primiparas delivered spontaneously or by vaginal operative procedure (excluding eight cases with incomplete records) we find that 1,088 were delivered spontaneously; twenty-two by median

TABLE III

	TOTAL	SPONTANEOUS	OPERATIVE	% OPERATIVE
O.L.A.	563	467	96	17.1
O.D.P.	437	364	73	16.6
O.L.P.	236	170	66	27.9
O.D.A.	105	87	18	17.1

indication. Maternal morbidity was about 3 per cent greater for occiput left posterior than for the other three positions. Spontaneous internal rotation occurred in about 94 per cent of occiput posterior as compared with not over 96 per cent of occiput anterior. Inasmuch as nearly half of the unrotated babies were delivered spontaneously without injury to the mother and without a single fetal death, the problem of failure of spontaneous internal rotation would seem to be not greater than 3 per cent for occiput anterior and 3.5 per cent for occiput posterior. Our present attitude toward occiput posterior is identical to our attitude toward occiput anterior, except that we realize that patience to the extent of about one hour more of waiting is required. Williams<sup>4</sup> has, previously, expressed a similar attitude.

### CONCLUSIONS

We should not want to give the impression that we believe that trouble is never encountered with occiput posterior. What we would like to point out is that trouble occurs with occiput anterior almost as commonly as with occiput posterior (3 per cent compared to 3.5 per cent). We also feel that inability of the patient to deliver herself spontaneously of an occiput posterior is due to causes other than the occipitoposterior presentation.

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### DISCUSSION

DR. J. C. LITZENBERG, MINNEAPOLIS, MINN.—When only a few cases are reported, from a statistical standpoint they are likely to be very unreliable, so percentages should not be employed in those small series. I would call attention to the fact that this series is fairly large, therefore any criticism of this statistical paper can be eliminated.

I commend this paper to you for study because it upsets many of the ideas we have had with regard to the length of labor. He has called particular attention to the increase of the first stage. His most impressive table, of course, is his table regarding spontaneous rotation. I think that Calkins has this morning substantiated the conclusion of the great master, J. Whitridge Williams, who said: "I have learned to approach a case of occipitoposterior with entire equanimity."

DR. JOSEPH L. BAER, CHICAGO, ILL.—The diagnosis of occiput posterior has carried two implications for us on the staff at the Michael Reese Maternity: First, the possibility of a somewhat slower first stage; and, second, the possibility that nonrotation and lack of progress in the second stage would require intervention. Spontaneous delivery of persistent occiput posterior, usually unrecognized, has occurred in our maternity often enough through the years to keep us from being stampeded when the diagnosis is made.

The critical analysis presented by Calkins demonstrates two things: The efficiency of his organization which has enabled him to gather such a mass of reliable data; and the soundness of his conclusions which place the stamp of authority on our own policy. The negligible difference between occiput posterior and occiput anterior in length of first and second stages, demonstrated by the essayist, is among the most striking of his findings.

local physician had tried for two hours to deliver the patient with forceps when the cervix was only 4 cm. dilated and then, after death of the baby, had sent the patient into our institution.

It might be pointed out that in 9 of the occiput right posteriors and 4 of the occiput left posteriors the low forceps delivery was done without rotation of the head, without serious trauma to the mother, and with no apparent injury to the baby. The delivery was easily accomplished in each of the 13 cases. (Respective birth weights: 2,565, 2,835, 2,865, 2,880, 3,025, 3,070, 3,100, 3,140, 3,175, 3,410, 3,425, 3,575, and 4,030 gm.)

In compiling these records we did not at first realize the importance of noting whether spontaneous internal rotation always occurred in the occiput anterior cases and hence the figures, above quoted, no doubt represent a somewhat more frequent occurrence of spontaneous internal rotation in occiput anterior than was actually the case. In the last two years we have noted that a number of these patients delivered without internal rotation. So far as this series shows, it would seem that spontaneous internal rotation occurred in about 96 per cent of occiput anterior and about 95 per cent of occiput posterior. Operative delivery is necessary, *perhaps because of failure of rotation*, in about 3 per cent of occiput anteriors and 3 to 3.5 per cent of occiput posteriors.

*Multiparas.*—Among the multiparas there were 4 O.D.A.'s, 3 O.L.A.'s, 5 O.L.P.'s, and 13 O.D.P.'s which either failed to rotate spontaneously or were delivered before rotation took place. Eighteen of these patients delivered spontaneously. There were 5 median forceps and 2 low forceps with only 1 fetal death and that, again, was due to an unsuccessful forceps before admission to the hospital. Failure of spontaneous internal rotation could not be said to have been a problem in more than 1 per cent of the multiparas in this series.

#### TIME OF SPONTANEOUS INTERNAL ROTATION

*Primiparas.*—A careful attempt was made to note the exact time at which internal rotation took place and in 1,138 patients out of the 1,364 the records showed rather clearly when rotation occurred. In 276 it was accomplished at or before complete dilatation of the cervix, in 398 during the descent of the head to the pelvic floor, in 393 only after the head had been on the pelvic floor for some time and in 71 spontaneous internal rotation did not take place. The proportion occurring at the various stages was roughly the same for all positions except O.D.A. where rotation was rarely produced until the head was on the pelvic floor or coming through the vulva. The fact that over 400 of the 1,364 patients did not show internal rotation until after the head was on the pelvic floor seems to us quite significant.

#### SUMMARY

Occiput posterior and occiput anterior occurred with about equal frequency in this series of 2,130 cases, where more than the usual care was taken to arrive at an early and accurate diagnosis. Occiput posterior was characterized by a somewhat longer first stage of labor. The difference, however, is not over one to one and one-half hours and the first stage in occiput right posterior is probably not much, if any, longer than in occiput anterior. The difference in the second stage is a matter of a few minutes only. Operative delivery, particularly low forceps, is more frequent in occiput left posterior than in the other three positions by about three cases in each one hundred. Fetal mortality is no greater in occiput posterior than in occiput anterior under the plan of management employed for this series. It should be noted that no pituitary extract was given previous to the delivery of the placenta and anesthesia was confined to nitrous oxide plus morphine on



## NEWER CONCEPTS OF BLOOD COAGULATION AND THE CONTROL OF HEMORRHAGE\*

EDWARD A. SCHUMANN, M.D., F.A.C.S., PHILADELPHIA, PA.

A PRIME factor in the mechanism of its production and the control of hemorrhage is the element of coagulation time of the blood.

With hemophilia at one end of the scale and the recently described disease thrombophilia at the other, coagulation time is seen to play the chief role from causing continuous bleeding on the one hand, to the production of scattered thrombi in otherwise healthy individuals on the other.

In traumatic hemorrhage coagulation time is also an important element, although naturally not so dominant as in the bleedings due to an inherent variation in this phenomenon.

It has long been recognized that, especially in hemorrhage of the capillary or venous type, the generalized oozing from raw surfaces during surgical operations, uterine mucosal bleedings and so on, reduction of the clotting time is of great value and hence investigators have studied many substances with this end in view.

Horse serum, moccasin venom, cephalin, and many other agents have been used to shorten clotting time with more or less uniformity in their action.

Recently Arthur Steinberg (Ph.D.) and W. R. Brown (Ph.D.) have been working on the problem of blood coagulation and have presented their findings in a paper read before the American Physiological Society at its 1939 meeting and entitled "A New Concept Regarding the Mechanism of Clotting and the Control of Hemorrhage." The statements immediately following are largely taken from the article alluded to. Extracts have been prepared from certain plants which have been found to accelerate the rate of the coagulation of the blood markedly and rapidly. The best plant sources have been found to be shepherds' purse, wood sorrel, beets, oxalis, citrus fruits, alfalfa, etc. These extracts have been biologically assayed in rabbits and a unit has been devised which is defined as the minimum amount of material which will reduce the coagulation time of a five-pound rabbit 50 per cent fifteen minutes after an intravenous injection. The extracts were found to be nontoxic in rats, rabbits and guinea pigs, contained no alkaloids or proteins and could be administered intravenously or intramuscularly without ill effects.

Similar extracts were prepared from placenta, cord blood, spleen, liver, bile, etc., which also possessed marked hemostatic properties.

From these preparations Steinberg and Brown isolated colorless monoclinic crystals, having a melting point of 100° C. and which possessed most of the clotting power of the extract. These crystals were identified as oxalic acid. Solutions of pure commercial oxalic acid were prepared in the same concentration as present in the extract and were found to possess the same power to reduce coagulation time in the rabbit as the extracts themselves.

A titrametric test for oxalic acid in the blood was devised and normal values for human beings were established at 5.5 to 7.5 mg. per 100 c.c. and for rabbits at

\*Read at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

In my opinion occiput posterior should be treated as a normal position so long as labor progresses and the parturient and fetus show no evidence of damage. To this I add one reservation. After one hour of second stage with little or no progress, I prefer rotation and forceps application for the actual delivery of the unrotated head.

Manual rotation is safer than forceps rotation for the average operator, especially in the primipara. Whether manual or forceps rotation is undertaken, its ease and harmlessness are greatly enhanced by initial upward dislodgement of the impacted fetal head.

DR. CALKINS (closing).—Dr. Baer and I find ourselves in quite substantial agreement in that after an occiput posterior has been in the second stage of labor one hour without substantial progress, we believe in interference. I think he would also take that stand with occiput anterior, so there is really no disagreement. In these 2,400 cases I presented that rule was followed.

amounts have been administered without any appreciable ill effects. The material is of value in hemorrhage of any type, but experience has shown that several modifications in administrative methods are necessary in certain types of bleeding.

In cases where hemorrhage is associated with increased permeability of the blood vessels as melena, the purpuric state, etc., the effect of koagamin is much enhanced if the patient be given massive doses of vitamin C for several days, preceding the exhibition of the coagulant in order to decrease the vessel permeability. When profound anemia is present, it is well to inject a donor with koagamin fifteen minutes before a blood transfusion, under which circumstances the maximum effect is obtained.

Koagamin has been extensively employed in the treatment of hemorrhage of various origins, hematemesis, bleeding gastric ulcers, jaundice, hemoptysis, hematuria, epistaxis, hemophilia, melena neonatorum and other forms of bleeding, with gratifying results.

I, naturally, have been especially interested in the use of this product in the management of hemorrhage arising from an obstetric and gynecologic service.

In hemorrhagic disease of the newborn, it has proved highly efficacious, an interesting demonstration having occurred in the obstetric division of the Philadelphia General Hospital. Identical twins were born, both suffering from hemorrhagic disease of the newborn; one baby was given mother's blood intramuscularly without benefit. The other received koagamin intravenously and intramuscularly, all evidence of hemorrhage ceasing within one-half hour. The first twin later was given the same preparation, after which it too stopped bleeding within a short time.

The use of this material has since become routine in all cases of melena neonatorum, arising in the services at Kensington and Chestnut Hill Hospitals, with excellent results.

In post-partum hemorrhage and in placenta previa, its action has been satisfactory, although more difficult to evaluate since bleeding of this type often ceases spontaneously. In a number of cases, we have observed that the bleeding of placenta previa diminished, even ceased, coincidentally with the sharp reduction of coagulation time brought about by koagamin. The action of this material can be well demonstrated if one has two plastic operations to perform during the same clinic. If one patient be given koagamin in the proper dose, fifteen minutes before operation, the other no special treatment, the difference in the bleeding of the operative field will be noteworthy. In the one case the dissection is almost dry, unless a spurting artery is cut, whereas in the other the usual venous ooze will be seen.

The question arises as to whether it is safe to use koagamin during the course of an operation, the fear being that subsequent relaxation may follow the wearing off of the effect of the drug. This has not been noted in our series of cases, because whenever koagamin is given during or im-

4.5 to 6.0 mg. per 100 c.c. Elevations in clotting time were attended by a fall in the blood oxalic acid, while reductions in clotting time resulted in a rise in the oxalic content of the blood. Cord blood was found to contain as much as 17 mg. per 100 c.c., while maternal blood immediately post partum also showed a considerable elevation in the blood oxalic acid. In both instances the clotting time was appreciably reduced.

Attempts to correlate the above findings with the work of Dorn, Schonheyder, Almquist and others, on the so-called vitamin K, have met with various degrees of success. Insufficient data are available to justify anything more than a brief statement that there appears to be a definite relationship.

In this work of Steinberg and Brown there appear certain significant facts.

It would seem that oxalic acid itself is a most potent agent in the mechanism of clotting. This is a somewhat surprising finding, since the use of salts of similar dibasic acids, notably citric in the form of sodium citrate, has been extensively used in connection with indirect blood transfusion for the very opposite purpose, namely to prevent or greatly retard clot formation.

The explanation of this reversed action of oxalic acid in vitro and in vivo is not yet clear and requires further elucidation, but the fact remains that the introduction of citrated blood into the circulation by transfusion is followed by a definite but slight decrease in coagulation time.

The exact action of oxalic acid in the physiologic process of blood clotting is still problematical, but it would seem that it acts as a catalyzer and adds to the function of calcium, platelets, and tissue juices in the formation of thrombin. Thus it may fit into the accepted formula for blood coagulation about as follows:

1. Prothrombin + Ca + oxalic acid + altered platelets  
|  
tissue juices  
= thrombin
2. Thrombin + fibrinogen = fibrin.

Steinberg has found that the introduction of a small amount of oxalic acid to the circulation steps up the formation of this substance already normally present, so that the oxalic acid level is increased far beyond the amount added to the blood.

#### CLINICAL APPLICATION

The extract from certain plant substances containing as its principal active agent oxalic acid, possibly with the little understood vitamin K, has been put up for the market under the name of koagamin, a sterile solution for intravenous and intramuscular administration. The oxalic acid content is 1 mg. per c.c. and the usual dose is 3 c.c. intravenously followed by 2 c.c. intramuscularly at intervals of from three to four hours. The effect on coagulation time becomes apparent after ten or fifteen minutes and lasts for about eight hours. Much larger

Steinberg's paper at Toronto at the meeting of the Society of Experimental Medicine and Biology, has sent me the following letter which I would like to include in this discussion:

I believe that Schumann's statement that oxalic acid is the active principle of vitamin K is probably a misunderstanding as I know of nothing that would tend to prove this. Vitamin K is chiefly of use in the bleeding tendency that sometimes develops in obstructive jaundice, and there is some evidence that it is effective in hemorrhagic disease of the newborn. Oxalic acid on the other hand seems to have been effective in a large variety of cases. I had the privilege of hearing Steinberg's paper recently at Toronto, and he did not link vitamin K with oxalic acid.

There were several questions which I wanted to ask Steinberg, among them being the method used for determining the decrease in coagulation time. Presumably they used the venous coagulation time, and in my experience this is a very unsatisfactory and unreliable method. Patients with a prothrombin deficiency, as in some cases of obstructive jaundice, may bleed considerably and yet have a normal venous coagulation time. The converse of this is true in hemophilia. I should like to know the effect of oxalic acid on the prothrombin content of the blood and on other factors concerned in blood coagulation, especially calcium?

Clinical observations of bleeding patients are notoriously untrustworthy unless all of the facts are known. Postoperative hemorrhage or oozing is usually treated by a variety of mechanical measures in addition to blood transfusions, and if a coagulant is administered in addition to the above measures, it is difficult to assign hemostasis to any single measure. Fortunately most postoperative hemorrhages, unless due to a known cause or a pre-existing condition, will stop spontaneously. I should like to know what other measures were tried and in what manner they failed.

Excessive menstrual bleeding or intrauterine hemorrhage is also due to a variety of causes and I should like to know the details of the previous or concurrent measures that were used in the treatment of these bleeding cases?

Dr. Randolph West of this hospital has used an extract of shepherd's purse (a plant extract recommended by Steinberg and Brown) on a case of hemophilia, and it was without significant effect.

Steinberg also states that cord blood contains as high as 17 mg. per cent of oxalic acid by the method of Suzuki, yet so far as I have been able to ascertain, the coagulation of cord blood is essentially normal by the commoner methods. There is considerable evidence that a low prothrombin level exists in cord blood and that hemorrhagic disease of the newborn is due to a prothrombin deficiency. It seems paradoxical that oxalic acid should prevent bleeding in blood which already contains three times the normal oxalic acid content.

It would seem fairly simple to produce a bleeding tendency in animals by either the use of heparin or by producing obstructive jaundice, and it would be of great interest to know if the blood oxalic acid content was inversely proportional to the coagulation time. The reduction of the coagulation time by 50 per cent is not unusual after simple venipuncture if the venous coagulation time method is used as the limits of normal values in this test are quite wide.

Numerous reports are available concerning the toxicity of oxalic acid, as it is a material commonly used for suicide. The symptoms are gastrointestinal, consisting of vomiting, diarrhea, and cramps—and neuromuscular, consisting of twitching of the muscles, tetany, convulsions, coma, and death. Certainly the widespread use of this material should not be advised without more careful study of its pharmacologic character and definite advice as to the amounts which may safely be administered.

mediately after the course of an operation its use is continued for from twenty-four to forty-eight hours, after which much danger of hemorrhage has usually ceased. In uterine bleeding, either of the functional type or, more particularly, the bleeding from fibroid tumors of the uterus, koagamin exerts an active influence. In fibromas the hemorrhage usually ceased within twenty minutes after the intravenous injection of the drug and, while it may recur, the quantity of blood loss has been definitely much less after the injection than before. Hemorrhage of functional origin yields also to this preparation in rather dramatic fashion, although the theoretically correct treatment of the hyperplastic endometrium with antuitrin-S should not be neglected. After difficult pelvic enucleations, the oozing raw surfaces in the cul-de-sac which are not capable of being covered by peritoneum may be rendered quite bloodless by the use of koagamin.

A patient now under treatment presents an interesting demonstration. A woman of 48 years had a massive hemorrhage from the urinary bladder, sudden in onset and without previous symptoms. The hemorrhage was so alarming that the patient's physician washed out the bladder with a saline solution in the hope of removing blood and with the idea that the solution might terminate the hemorrhage. This proved unavailing and the patient was referred to Kensington Hospital for Women. Immediate blood transfusion was performed and then an attempt to visualize the bladder mucosa by the cystoscope was made and was unsuccessful, there being far too much active hemorrhage to utilize this instrument. Koagamin was administered, 3 c.c. intravenously and 2 c.c. intramuscularly every four hours thereafter. The bleeding continued for about two hours and was then reduced to a pinkish serous flow, but the patient complained of increasing vesicle pain and great tenesmus. Forty-eight hours later another attempt at cystoscopy proving abortive, the bladder was incised through the anterior vaginal wall with the idea of direct inspection of its interior. A huge, very firm blood clot with urinary crystallization beginning upon its surface was extruded from the bladder; the clot on examination was firm and tenacious and could be pulled apart only with difficulty. The bleeding did not recur and the patient is awaiting the subsidence of her acute cystitis before further investigation as to the cause.

The above scattered instances will serve to illustrate the uses of this new preparation on the gynecologic and obstetric services. Whether continued acquaintance with its properties will alter the convictions of the staff as to its efficacy in controlling hemorrhage cannot be stated, but it is true that at the present time the entire service is enthusiastic concerning it.

#### REFERENCE

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1814 SPRUCE STREET

#### DISCUSSION

DR. WILLIAM E. CALDWELL, NEW YORK, N. Y.—I am sure none of us is prepared at this time adequately to discuss the findings of Schumann and his co-workers. It is rather startling to find a drug which is frequently used for suicidal purposes, and which has so long been considered an anticoagulant rather than a coagulant, advocated in the control of bleeding.

Kenneth B. Olsen of the Department of Surgery, Presbyterian Hospital, who has been working on the problem of the coagulation of the blood and who had heard

# ELECTRICAL AND MECHANICAL ACTIVITY OF THE HUMAN NONPREGNANT UTERUS\*

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(From the Laboratory for Clinical Physiology, Chicago; and from the Department of Gynecology and Obstetrics of Michael Reese Hospital)

THE human uterus has not yet been studied by the extremely sensitive methods now open to the electrophysiologist. Accordingly, we have sought to make an introductory survey in this field, limiting our efforts to the nonpregnant organ under normal and certain pathologic conditions. We have secured mechanical tracings simultaneously, as an aid to the first interpretation of the electrical records. This has required us to develop a particularly sensitive air recording system connected with a bag in the uterus filled only with air.

Contractions have been registered by mechanical contrivances by various workers including Schatz,<sup>1</sup> Knaus,<sup>2, 4</sup> Moir<sup>5</sup> and one of us (J. E. L.<sup>6-8</sup>). Contractions can also be registered by electrical methods as developed by one of us (E. J.<sup>9</sup>) in 1930 for human skeletal muscle, even if the contraction is microscopic in extent. Limits of space preclude an historical account of the electrical studies on smooth muscle made by Matteucci,<sup>10</sup> Fuchs,<sup>11</sup> Poá<sup>12</sup> and others. In later years uterine contraction voltages† have been studied in the guinea pig, cat, rat, and other mammals.<sup>13-20</sup>

Contraction voltages in the human uterus have been studied by Theilhaber,<sup>21</sup> Veit,<sup>22</sup> Bode<sup>23</sup> and Falk and Nahon.<sup>24</sup> These studies may be regarded as introductory only, for in our opinion the electrodes have not been of suitable metal, nor have they been placed properly for reliable records, while the apparatus employed (the string galvanometer) is not sufficiently sensitive to obtain records from voltages present in many women.

## METHODS AND PROCEDURE

1. *Electrical Instruments.*—For the present studies, two string galvanometers were available. The string tension on one (Sanborn) was set at 1 cm. per 3 millivolts; on the other (Cambridge) 1 cm. per 4 millivolts. Tension higher than in electrocardiography is employed in order to render the response to higher frequencies more accurate. With the tension as stated, the characteristic is flat up to about 200 cycles at least.

By means of a switchboard any one of three amplifiers could be thrown in circuit with either galvanometer. These assemblies have been described previously (Jacobson, 1930, 1931)<sup>25, 26</sup> except for certain im-

\*Presented at a meeting of the Chicago Gynecological Society, May 19, 1939.

The generous cooperation of the Bell Telephone Laboratories is again gratefully acknowledged.

†The customary term is "action-potentials." We propose instead "contraction voltages" for the potentials in electrodes in muscle tissue associated with contraction.

In conclusion, again, the proof of the pudding is in the eating. A very careful conservative man has advocated the use of oxalic acid in controlling bleeding. The many theoretical questions which come up must be answered in time and, in spite of Schumann's results, I would urge extreme conservatism in its universal use, until the many questions have been answered by the complete paper and independent research.

DR. SCHUMANN (closing).—I cannot answer these statements in the discussion read by Caldwell as many of them are obviously made without knowledge of the experimental facts which have been set forth in my paper and which are based on a large number of experiments.

With regard to the danger of oxalic acid, I may say that this drug has been given to something over 1,200 patients, often in repeated doses. Not only have no deleterious effects been observed, but we have not yet noted a single reaction of any sort. I therefore feel that the danger is negligible.

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the rubber facing carried a very fine hook, connected by a short length of inelastic fiber to a wheel which moved with a lever mounted on a shaft on jewel bearings, counteracted by a damping spring. This assembly (which can magnify about seventyfold) had been used for other purposes in previous studies (Jacobson,<sup>28</sup> 1930). The lever moves freely in the horizontal position, but its free terminal was bent vertically, so that its movements made a shadow on the photographic record.

By-pass tubes with stopcock arrangements made it possible to inflate the balloon after it was in the uterus, using an air syringe, while the pressure in the system could be tested with an oil manometer. As a rule, when used most sensitively, the pressure was approximately equal to a column of water 95 cm. in height.

Leakage of air was tested for carefully before the experiments. It was avoided in later tests, but not always in the earlier ones, some of which had to be discarded.

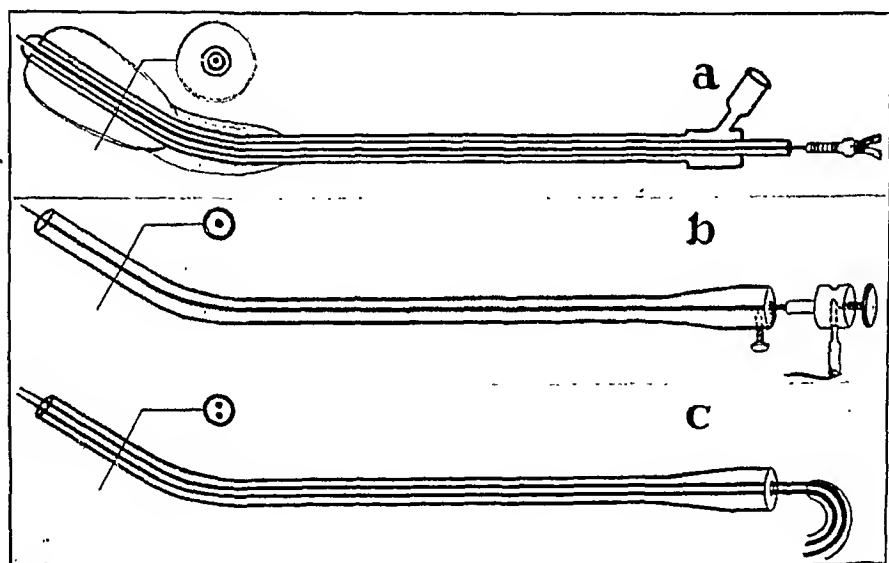


Fig. 1.—Catheters containing wire electrodes for insertion into the corpus uteri (*a*) with and (*b*, *c*) without a bag.

The platinum-iridium wires appearing in black in Fig. 1, *a* are freely movable and are completely insulated with bakelite varnish everywhere excepting at the tip. During insertion the wire or wires lie entirely within the containing sheath (metal in *a*, leather in *b* and *c*); but when the sheath makes contact with the inner wall of the fundus, the wire can be pushed out into the fore end of the corpus. The number of millimeters of protrusion is determined by the scale marked by a wire on the handle.

4. *Rooms*.—The laboratory is provided with a separate, shielded room for the patient and the couch on which she lies. Amplifiers and standardizing devices are concealed within the couch. Leads from the patient pass to wall plates connected with an elaborate switchboard in another room—the instrument room, containing the galvanometers. Similarly

provements which cannot be outlined for lack of space. "Amplifier 1" is of the resistance-capacity type. Upon the application of a steady voltage to the input, the string deflection declines to zero in about four seconds. "Amplifier 2" and "Amplifier 3" are transformer coupled, capable of recording higher frequencies only: from about 30 to 4,000, they show a flat characteristic. In place of 1 cm. deflection per millivolt, they make it possible to secure, when needed, 1 cm. deflection per microvolt. The voltage sensitivity available is therefore one thousand times that of the string galvanometer alone. Any lesser sensitivity needed can be secured at will by a shunt (1-10,000 ohms) placed across the string terminals.

2. *Electrodes*.—In order to record uterine contraction potentials reliably, electrodes should penetrate into the uterine tissue. This secures not alone direct contact, but avoids potentials due to differential action of fluids in the uterine cavity or other space containing the electrodes. In addition, the uterine tissue acts as a thermostat, averting thermal potentials which otherwise prove confusing if delicate measurements of transient potentials are attempted.

Platinum-iridium wires, with points sharpened for penetration have been described previously (Jacobson, 1933).<sup>27</sup> The wire is pushed into the tissue for about 5 to 6 mm. or more. No wire is exposed, for what does not lie within the tissue is covered with insulating material.

The purpose of using such wire electrodes is to secure a record of potentials in them resultant from electrical pressures in a considerable portion of adjacent muscle fibers. (Concentric electrodes were used in one study only.) The following combinations of localities were employed: (A) *Two electrodes in the fundus musculature, a few millimeters apart* (Fig. 1, c). (B) *One electrode in the fundus musculature, with the other in the cervix* (Fig. 1, a or b). (C) *Both in the cervix*. In all instances the wires are inserted to the insulated hilt.

The electrode connected with the grid of the first tube in Amplifier 1 or with the inner part of the winding of the input transformer when either Amplifier 2 or Amplifier 3 is used is arbitrarily called "positive." This electrode is always the one inserted into the fundus musculature when the other is inserted into the cervix.

In addition, during certain studies on the uterus, simultaneous electrical records were taken with platinum-iridium wire electrodes inserted to the insulating hilt into the (skeletal muscle of the) abdominal wall.

3. *Mechanical Records*.—A deflated balloon was inserted into the fundus cavity for many tracings. This was conveniently assembled into the same device as carried the electrode which was inserted into the fundus musculature (Fig. 1, a). Flexible tubes provided passage of air currents from the inside of the balloon to the inside of a disc-shaped hollow container, the open face of which was covered with a sheet of Penrose rubber, after the pattern of a Marey tambour. This rubber was like that in the balloon. A tiny metal disc glued to the center of

Quiescent periods often varied from about thirty seconds to nine minutes; the beginning of one is illustrated in the terminal portion of the tracing shown in Fig. 2, *a*. The first contraction would then appear, but relatively small, followed perhaps in two seconds by a second contraction, equally small or a little larger; then as if the mechanism had become started, successive contractions would come at briefer intervals, generally a small fraction of a second, and in stronger form. About thirty-one contractions appeared in one series; but the number varied considerably and the amplitude of the contraction in one series would differ considerably from that in another. It is convenient to classify and to present the illustrative data in women according to the locations of the electrodes.

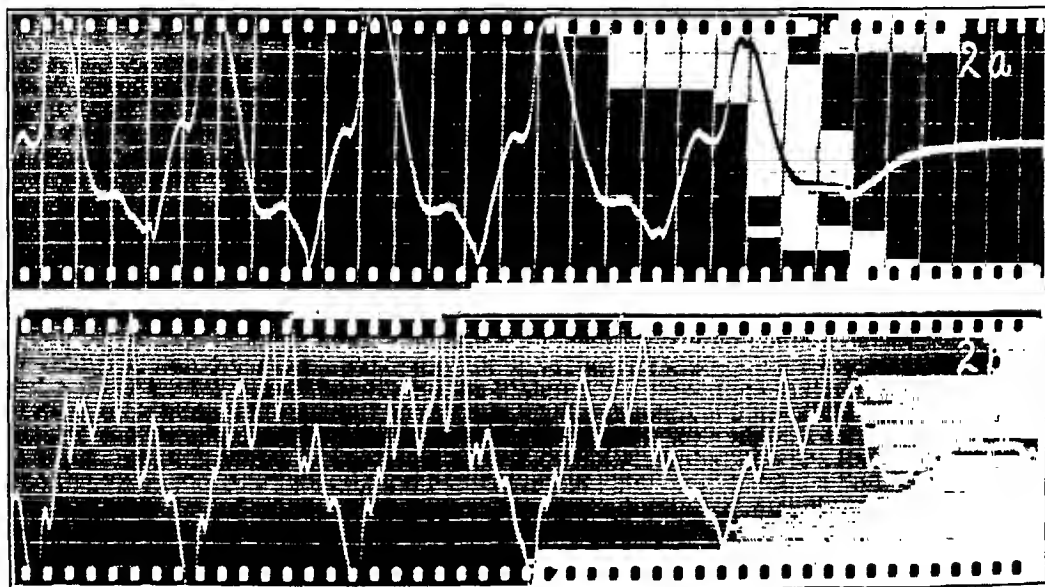


Fig. 2.—*a*, This photographic record of contraction voltages illustrates a period of regular recurrence at about 1 per second. Interval between vertical time lines = 0.2 second in this and in all subsequent figures. Read from left to right in all figures. 1 cm. = 0.8 millivolt. Amplifier 1. The control test, when a short-circuit exists across the input terminals of the amplifier, is a straight horizontal line. *b*, Contraction voltages at another time, 1 mm. = 4 microvolts ( $\mu$  v.). When a short-circuit exists across the input terminals of the amplifier, the string is approximately quiet.

#### *Uterograms, Type A.*—Two electrodes in fundus tissue:

CASE 1.—D. B., aged 22 years, had been married six months. Menstruation was irregular; last period profuse, ended three days previously. Physical examination, including bimanual examination, was negative. Two platinum electrodes were inserted directly into the body of the uterus (Fig. 1, *c*). We present a recording with the string galvanometer direct (Fig. 3, *a*), with Amplifier 1 (Fig. 3, *b*).

In contrast with the nonpregnant dog mentioned above, quiescent periods do not exceed two seconds; they frequently last about 0.5 second. During control tests, with conditions identical, except that the tips of the electrodes have been withdrawn a few millimeters into the leather sheath, still lying within the uterine cavity, the results are negative, i.e., no deflection is shown by the galvanometer string (Fig. 3, *c*). The findings confirm the view that the human nonpregnant uterus undergoes spontaneous contractions, at least at times. The objection is answered that such contractions are perhaps due to a bag, acting as a stimulating foreign body within the

the air tube passes from the patient to connections through the wall with the mechanical recording devices in the instrument room. In this manner, the patient is kept free from disturbance by the movement and speech of the operators.

5. In all, twenty-nine women have been studied. In planning an introductory survey, our aim was to secure something like a random sampling at various ages and at various times of the menstrual cycle in normal individuals as well as in some diseased conditions. We did not seek to make an exhaustive study of any one condition or of contractions at all of the stages of the menstrual cycle.

In Table I and Table II are presented pertinent data concerning these patients.

TABLE I

Total No. cases	29
Total No. experiments	34
Age variation	19 to 51
Parity (average)	2.2
Time of cycle	
First half (patients)	10
Second half	9
Menstruating	2
Irregular	5
Postmenopausal	1
Posthysterectomy	1
Post partum (6 weeks)	4

TABLE II

Present Complaints:	NO. OF PATIENTS
Vaginal discharge	9
Abdominal pain	8
Irregular menses	4
Menorrhagia	4
Backache	4
Premenstrual nervousness	4
Dysmenorrhea	1
Pruritus vulvae	1
Dyspareunia	1
Sterility	1
Abnormal Pelvic Findings:	
Retroverted uterus	4
Chronic endocervicitis	4
Chronic adnexitis	3
Fibroid uterus	2
Prolapsed ovary	1

## RESULTS

For purposes of comparison with human records, tracings from the virgin uterus of a dog are shown in Fig. 2. Two fine platinum wire electrodes are inserted into the left horn of the exposed uterus. Operation had been performed previously by Roy Templeton. The wound had healed perfectly. No anesthetic was needed, for the dog evidently was not disturbed by the electrodes. Some of the spontaneous contractions were sufficiently large to be grossly visible before the electrodes were inserted, while others could not be seen, but were recorded clearly.